The Emerging Therapeutic Role of Medical Foods for Gastrointestinal Disorders

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Keywords
Medical foods, EnteraGam, VSL#3, Modulen IBD, Vivonex

Abstract: In addition to drugs approved by the US Food and Drug Administration (FDA) that treat, cure, or mitigate disease, medical foods are a tool to help manage chronic conditions and diseases. A medical food, according to the FDA, is a food that is developed to be eaten or administered enterally under the guidance of a physician and that is meant for the specific dietary management of a condition or disease for which distinctive nutritional requirements, based upon known scientific principles, are established by medical evaluation. A variety of medical foods exist to help manage a wide range of medical conditions, from Alzheimer disease to HIV-associated enteropathy. EnteraGam contains serum-derived bovine immunoglobulin/protein isolate, which has been studied extensively in diarrhea-predominant irritable bowel syndrome, inflammatory bowel disease (IBD), and HIV-associated enteropathy. VSL#3 is a probiotic that is used in pouchitis for patients with ulcerative colitis as well as irritable bowel syndrome. Modulen IBD is a whole-protein, sole-nutrition formulation used to manage the active phase of Crohn's disease. Vivonex is an elemental diet that is used in a variety of diseases associated with severe gastrointestinal dysfunction. Medical foods are safe and must have proven efficacy in helping to manage a variety of gastrointestinal conditions and diseases. These therapies represent tools that can be used prior or in addition to traditional medical therapies. This article discusses the history and development of medical foods under the FDA and concentrates specifically on medical foods used to help manage diseases of the gastrointestinal tract.

Drug therapies have gone through an evolution of development. Most drugs were originally purified from natural sources and approved only for safety, as opposed to drugs today, which are new molecular entities to which humans have never been exposed. Newer drugs, which tend to have very specific targets to modify disease progression, require extensive testing to ensure some level of safety and efficacy in humans. However, medical therapies do not necessarily have to be targeted toward specific receptors, proteins, and metabolic pathways in order to modify biologic pathways at different levels. Food, for example, provides essential

nutrients and natural compounds that alter the history of certain diseases and conditions safely and effectively. When purified, natural ingredients can be safely used to manage chronic conditions and diseases.

Medical foods, or purified food ingredients, are based on the idea that diseases can be safely managed with compounds that humans have adapted to over millennia. The medical food industry is now a multibillion-dollar business, with hundreds of product launches worldwide over the past few years.[1] Medical foods are available to manage a wide range of diseases, including Alzheimer disease,[2,3] osteoporosis,[4-6] venous insufficiency,[7] and a variety of enteropathies.[8-11] This article focuses on the history and definition of medical foods and highlights certain medical foods that target conditions and diseases of the gastrointestinal tract.

History and Evolving Definition of Medical Foods

Prior to 1938, medications did not require rigorous scientific study to prove efficacy and safety. Proprietary elixirs with questionable efficacy, some with dangerous side effects, were often touted as cure-alls. The US Federal Food, Drug, and Cosmetic Act was passed into law in 1938 under President Franklin D. Roosevelt, replacing the Pure Food and Drug Act enacted in 1906. The 1938 act was passed to oversee the safety of all foods, drugs, and cosmetics. In 1941, an amendment to this act created the category of foods for special dietary use to treat a variety of pathologic, physical, physiologic, or other conditions.[1,12]

After 1941, foods for special dietary use with medical claims were required to undergo the same rigorous scrutiny as drugs do for safety. The majority of these formulations treated inborn errors of metabolism that required specialized dietary restrictions, such as Lofenalac for phenylketonuria.[12,13] Because conditions such as phenylketonuria are rare, the medical foods used to manage them were classified as orphan drugs, as they were designed to treat conditions that affect fewer than 200,000 US citizens. The passage of the Kefauver-Harris Drug Amendments in 1962 required drugs to be approved by the US Food and Drug Administration (FDA) for safety and efficacy. Although FDA approval is intended to reassure medical providers and patients that products are safe and efficacious, dozens of drugs have been removed from the market and box warnings have been issued over the past 5 decades due to safety problems that did not arise until the drugs were widely used in patients. In 1972, the laws governing medical foods were relaxed to allow for wider distribution and to foster creativity in the development of new products. The following year, medical foods became exempt from the labeling restrictions that were required for conventional foods purchased in stores for nutritional and medical claims because medical foods do not necessarily always have sugar, fat, protein, salt, vitamins, and minerals.[12]

The term medical food was not explicitly defined in federal law until 1988 under the Orphan Drug Act as a food that is intended to be consumed or enterally administered under the direction of a physician and that is formulated for the specific dietary management of a condition or disease for which distinctive nutritional requirements, based upon known scientific principles, are established by medical evaluation. The FDA continues to oversee the medical food industry and maintains annual inspections of production facilities.[14] Recently, the FDA increased scrutiny on medical foods and suggested a narrow definition through nonlegally binding guidance documents rather than regulation. The most recent FDA guidance documents regarding medical foods were drafted in 2013 and finalized in 2016.[15] The FDA states that a product is a medical food if (1) the product is a food for oral or tube feeding; (2) the product is labeled for the dietary management of a medical disorder, disease, or condition; and (3) the product is labeled to be used under medical supervision and is primarily obtained through hospitals, clinics, and other medical and long-term care facilities.

Medical foods cannot be whole foods, such as those purchased at a grocery store. Rather, they must be specially formulated to a point that a patient cannot obtain the same medically determined nutrient requirements by the modification of the normal diet alone. In addition, medical foods must be administered under the supervision of a physician to ensure proper use for the condition or disease for which they are provided. Although chart orders and prescriptions are the traditional manners in which medical foods are provided to patients, a prescription is not strictly required since medical foods cannot be labeled prescription only, which is something exclusive to drugs. The FDA requires that medical foods be administered to a "patient receiving active and ongoing medical supervision (eg, in a health care facility or as an outpatient) by a physician who has determined that the medical food is necessary to the patient's overall medical care."[8] Furthermore, medical foods cannot be used for a condition that can be managed with simple adjustment of the normal diet, such as diabetes or vitamin and mineral deficiencies.[15]

Medical foods include nutritionally complete formulas; nutritionally incomplete formulas containing proteins, carbohydrates, or fats; formulas for metabolic disorders in patients over 12 months of age; and oral rehydration formulas.[14] These foods differ from dietary supplements and FDA-approved drugs in a number of

Table 1. Comparison of Medical Foods to Dietary Supplements and FDA-Approved Drugs

	Medical Foods	Dietary Supplements	FDA-Approved Drugs
Targeted Population	Patients with a chronic condition or disease	Healthy people	Patients with a chronic condition or disease
Use	Management of chronic conditions or diseases	Support of healthy structure and function	Treatment, mitigation, or curing of chronic conditions or diseases
Scientific/Clinical Data	Required to substantiate use	No data required	Required to prove use
Safety	Must be generally recognized as safe by expert panel review	No data required	Must be proven safe through phase 1, 2, and 3 clinical testing
Efficacy	Clinical trials are required to substantiate use	No data required	Must be proven safe through phase 2 and 3 clinical testing
Route of Administration	Oral	Oral or enteral	Any route
Medical or Physician Supervision	Required under federal and state statutes	No supervision required	Required under federal and state statutes
Establishing Act of Congress	Orphan Drug Act (1988 amendments)	Dietary Supplement Health and Education Act of 1994	Federal Food, Drug, and Cosmetic Act (1938 to present day)
FDA-Approved or -Regulated	Regulated	Regulated	Approved

FDA, US Food and Drug Administration.

Adapted from Morgan SL, Baggott JE[86] with permission.

ways that are summarized in Table 1. The main difference between medical foods and dietary supplements is that medical foods are used to manage a chronic disease or condition under medical or physician supervision, whereas supplements are intended for healthy individuals and can be obtained over-the-counter (OTC).

The use of medical foods for specific diseases must also be supported by recognized science. According to the Orphan Drug Act as well as regulatory writings and warning letters from the FDA, each medical food product should have peer-reviewed, published information on the distinctive nutritional requirement provided by the medical food for the specific condition or disease, as well as peer-reviewed, published clinical studies to support label claims and intended use(s). There are no such requirements for dietary supplements. Medical foods require safety reviews by panels of toxicologists and must be generally recognized as safe for consumption, although phase 1, 2, and 3 trials are not required.

Medical foods exist for a variety of conditions. Some examples are listed in Table 2. This article focuses on medical foods that impact diseases and chronic conditions of the gastrointestinal tract, including EnteraGam (Entera Health, Inc), VSL#3 (Sigma-Tau Healthscience USA, Inc), Modulen IBD (Nestlé Health Science), and Vivonex (Nestlé Health Science).

Possible Mechanisms of Action of Medical Foods for Gastrointestinal Disorders

Each packet of EnteraGam is composed of 5 g of serum-derived bovine immunoglobulin/protein isolate (SBI) purified from edible plasma approved by the US Department of Agriculture, 5 g of pure dextrose (glucose) to help the protein dissolve in liquids or soft foods, and trace amounts of sunflower lecithin, a healthy fat molecule used in spray drying the product. SBI is approximately 92% protein, of which more than 50% is immunoglobulin (Ig) G, 5% IgM, 1% IgA, and 5% bovine serum albumin and other proteins that reflect the composition of plasma. The primary mechanism of SBI in this formulation is to maintain the integrity of the microbiologic, physical (tight junctions), and immune barriers of the gut. SBI is thought to bind microbial degradation components, thereby increasing their size to such an extent as to prevent access to the lamina propria by steric exclusion, similar to the action of secretory IgA (Figure). Thus, by excluding microbial components, SBI maintains immunologic balance in the gastrointestinal tract, manages gut barrier function with normal tight junction protein expression in the gastric mucosa, and improves nutrient as well as water absorption.[16] It is important to note that SBI is not systemically absorbed and metabolized by the hepatic

Table 2. Various Medical Foods Currently Available

Trade Name	Disease or Chronic Condition	Health Claim
Cerefolin NAC	Mild to moderate cognitive impairment with or without vitamin B12 deficiency, vascular dementia, or Alzheimer disease	Dietary management of patients being treated for early memory loss, with emphasis on those at risk for neurovascular oxidative stress and/or hyperhomocysteinemia
Axona	Alzheimer disease	Management of metabolic processes associated with mild to moderate Alzheimer disease
Vasculera	Chronic venous insufficiency	Clinical dietary management of the metabolic processes of chronic venous insufficiency
Fosteum PLUS	Osteopenia and osteoporosis	Clinical dietary management of the metabolic processes of osteopenia and osteoporosis
EnteraGam	Chronic loose and frequent stools	Clinical dietary management of the nutrient needs of patients with chronic loose and frequent stools (IBS-D, IBD, HIV-associated enteropathy, malnutrition)
Modulen IBD	Crohn's disease	For use as a sole source of nutrition during the active phase of Crohn's disease and for nutritional support during the remission phase
VSL#3	IBS-D and pouchitis	Clinical dietary management of IBS-D and pouchitis
Vivonex	Severe protein or fat malabsorption, transitional feeding, extensive bowel resection, malabsorption syndrome, select trauma/surgery, early postoperative feeding, intestinal failure, pancreatitis, chylothorax, trophic feeding, TPN alternative, dual feeding with TPN	For nutritional support of those with severe gastrointestinal impairment

IBD, inflammatory bowel disease; IBS-D, diarrhea-predominant irritable bowel syndrome; TPN, total parenteral nutrition.

or renal organs as a whole protein source, although it is slowly digested to the amino acid level as it passes down the digestive tract. Orally administered Ig from human and bovine sources has been shown to survive the length of the digestive tract out to the feces.[17] Along with diarrhea-predominant irritable bowel syndrome (IBS-D), SBI has been studied in the management of other chronic diseases such as HIV-associated enteropathy and inflammatory bowel disease (IBD).

VSL#3 is a probiotic composed of 4 strains of *Lactobacillus* (*L acidophilus* DSM 24735, *L delbrueckii* subsp. *bulgaricus* DSM 24734, *L paracasei* DSM 24733, and *L plantarum* DSM 24730), 3 strains of *Bifidobacterium* (*B breve* DSM 24732, *B infantis* DSM 24737, and *B longum* DSM 24736), and 1 strain of *Streptococcus* (*S thermophilus* DSM 24731). Probiotics are thought to work by providing healthy and safe bacteria to the gastrointestinal tract. This may modify the gut microbiota mix and allow the probiotic bacteria to compete for adherence to the mucosa and epithelium and increase mucus production while modulating the host-immune response by interaction with toll-like receptors to maintain a gastrointestinal-immune balance.[18]

Modulen IBD is a whole-protein, casein-based, nutritionally complete (containing fat, sugar, vitamins, and minerals) polymeric formulation enriched in transforming growth factor-beta (TGFβ). Modulen IBD may work by a direct anti-inflammatory effect of TGFβ but also through a prebiotic effect of supporting growth of commensal bacteria.[19] In addition, the formulation has been shown to promote a healing reaction in IBD.

Elemental enteral formulations that contain 100% free amino acids, such as Vivonex, are thought to work in a variety of ways to assist in IBD management. Among the proposed mechanisms of action, elemental diets are thought to decrease gut permeability, reduce the work of digestion, lower dietary antigens, and beneficially alter the intestinal microbiome. Reduction of inflammatory cytokines is another major mechanism by which elemental enteral nutrition helps control IBD.[20]

EnteraGam

Although the exact etiologies of diseases such as IBS-D and IBD are not known, it has long been recognized that a combination of factors, including gastric mucosal

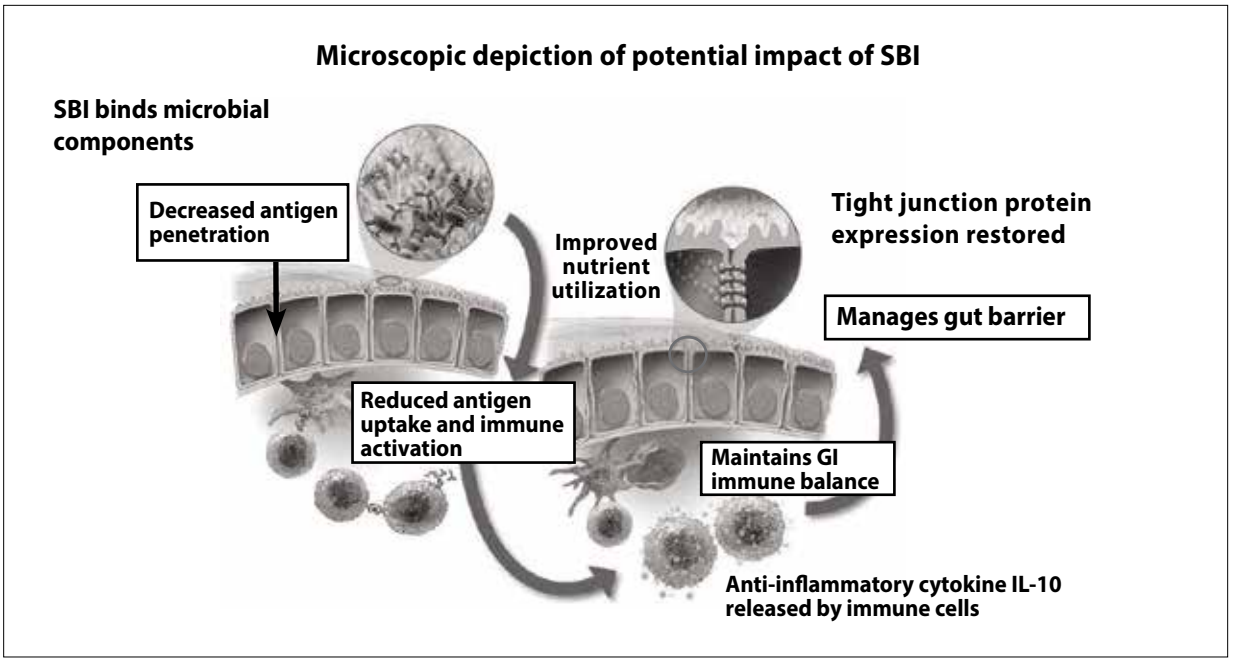

Figure. The mechanism of serum-derived bovine immunoglobulin/protein isolate (SBI) in the management of gastrointestinal (GI) conditions and diseases.

IL, interleukin.

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immune system activation and changes in the composition of natural gut microflora, are likely contributors to their overall pathogenesis.[21] The fecal microbiota of irritable bowel syndrome (IBS) patients differs significantly from that of healthy subjects.[22,23] SBI in EnteraGam has been extensively studied in IBS-D, HIV-associated enteropathy, and IBD. It is understood that proteins such as Igs are essential for the creation of the intestinal microbiota barrier and maintaining gut homeostasis.

Diarrhea-Predominant Irritable Bowel Syndrome

In regard to IBS-D, there have been multiple studies evaluating the efficacy of SBI. In 2015, a retrospective case series by Shafran and colleagues evaluated 28 subjects with refractory IBS-D who reported up to 82% improvement in symptoms.[24] Multiple other retrospective studies have shown promising results of SBI as a modality for IBS-D.[25-28] In a randomized, double-blind, placebo-controlled trial, 66 subjects with IBS-D were administered either 10 g of SBI daily, 5 g of SBI plus 5 g of soy protein isolate daily, or 10 g of soy protein isolate (placebo) daily for a total of 6 weeks.[29] The 3 study arms were monitored for the improvement of symptoms such as loose stools, bloating, abdominal pain, or fecal urgency. Statistically significant symptom reduction of all symptoms (all $P<.05$) was achieved in the cohort receiving 10 g of SBI daily, including the IBS-D defining symptoms of abdominal pain and loose stools between week 2 and week 6. Within the cohort receiving 5 g of SBI plus 5 g of soy protein isolate, there was also significant improvement of the composite score for IBS-D symptoms for flatulence ($P=.018$) and incomplete evacuation ($P=.020$). Of note, there was no significant symptom improvement in the placebo group for any symptoms.

HIV-Associated Enteropathy

The incidence of HIV-associated enteropathy is estimated to be 30% to 50% of patients on highly active antiretroviral therapy (HAART).[30,31] HIV-associated enteropathy is defined as chronic diarrhea for more than 4 weeks without any inflammatory or infectious etiology in a patient with HIV. The exact pathogenesis of HIV-associated enteropathy is not known. However, it has been postulated that HIV infection of gastric cells impairs nutrient breakdown and absorption. Increased inflammation in infected gastric cells alters permeability and barrier function, resulting in diarrhea. Importantly, HAART itself has been reported to be a culprit of chronic diarrhea and enteropathy. HIV-associated enteropathy is a diagnosis of exclusion in patients with HIV on HAART. Diagnosis is usually made when all other causes, including infection, are ruled out. Currently, the only FDA-approved treatment for HIV-associated enteropathy is crofelemer (Mytesi, Napo Pharmaceuticals), a natural, plant-derived

proanthocyanidin mixture that inhibits intestinal chloride channels. Crofelemer was effective in 17.6% of clinical trial patients compared to 8% receiving placebo.[32] An early open-label study of SBI found that patients with severe HIV-associated enteropathy had significant symptom and quality-of-life improvements with SBI as well as increases in CD4+ counts in the duodenum.[33] In a follow-up, placebo-controlled, large, multicenter (n=10) study, 103 subjects were randomized to receive 2.5 or 5 g of SBI twice daily compared with placebo during a 4-week lead-in phase, followed by 2.5 or 5 g of SBI twice daily for 20 weeks.[34] This study found that SBI administration led to a statistically significant increase in peripheral CD4+ cells after 4 and 24 weeks among subjects in the lowest quartile (<418 cells/mL) compared to patients administered placebo and to baseline numbers. In addition, duodenal biopsies confirmed previous study results of increases in mucosal CD4+ cells and CD4+/CD8+ ratios. The study also found a significant decrease in interleukin (IL)-6 and a correlation between change in intestinal fatty acid binding protein (iFABP, a marker of intestinal and enterocyte damage) and flagellin levels at week 8 (P=.028) and week 24 (P=.042) in subjects with the lowest quartile baseline CD4+ counts. Likewise, there was a trend in correlation between serum IL-6 and zonulin levels at week 24 (P=.064) in subjects with the lowest quartile baseline CD4+ counts. The results for flagellin, zonulin, and IL-6 suggest that the mechanism of microbial component binding and exclusion (flagellin in this case) leads to significant immune reconstitution in this patient population.

Inflammatory Bowel Disease

IBD is divided into 2 main disease states: Crohn's disease and ulcerative colitis (UC). Crohn's disease may involve the entire gastrointestinal tract, and transmural rather than mucosal inflammation is seen. In contrast, UC involves the colon, and inflammation is seen in the superficial layer of the gastrointestinal mucosa. At the moment, there is no cure for either disease state, and treatment is focused on symptom and disease control. The goal of therapy is to reach complete remission, which includes symptom management, normal mucosal appearance, and evidence of histologic tissue healing by biopsy. Current medication regimens aim to suppress the immune system by blocking its activation at different sites, including tumor necrosis factor-alpha (TNFα). Initial studies have shown promise regarding the use of SBI in IBD patients who have been refractory to pharmacologic management, including immune modulation and immunosuppression.

The support for the use of SBI in EnteraGam in IBD comes from 2 classic animal models of UC. The first model demonstrated that SBI statistically attenuated tissue damage in the cecum and colon, decreased secretion of cytokines and chemokines from cecal biopsies, and reduced systemic circulation of iFABP and serum amyloid A in plasma utilizing an *Escherichia coli* LF82/dextran sodium sulfate–induced colitis in mice.[35] In the second model utilizing a knockout mouse ($mdr^{-/-}$) that develops spontaneous colitis, SBI statistically blocked colon crypt permeability; prevented a reduction in tight junction protein expression; and decreased TNFα, interferon-γ (IFN-γ), and inducible nitric oxide synthase expression.[36] In addition, SBI attenuated the decrease in goblet cells and was statistically correlated with increased mucin-2 and trefoil factor-3 expression. These effects suggest that SBI blocks changes in colonic barrier function alterations in the spontaneous colitis model.

In humans, the primary data supporting EnteraGam use in IBD are from retrospective case series in a relatively small number of drug- and biologic-refractory patients,[37] with the largest case series (n=38 Crohn's disease and n=7 UC) demonstrating that the addition of EnteraGam to current therapy led to clinical remission in patients with long-term histories of disease not managed by other therapies.[38] There is also evidence of mucosal healing from 2 different retrospective case studies.[39,40] Case study evidence also found that 9 of 10 pouchitis patients who failed to respond to conventional therapy (antibiotics and probiotics) did not achieve clinical, asymptomatic remission of their condition until the addition of EnteraGam.[41] Similarly, a 13-year-old UC patient on corticosteroids (prednisone and budesonide), 6-mercaptopurine, mesalamine, and VSL#3 entered remission only when EnteraGam was added to therapy.[42] In addition, fecal calprotectin monitored in this patient demonstrated a reduction from over 1700 μg/g to baseline (<15 μg/g) after the addition of EnteraGam to therapy, suggesting a quiescent inflammatory state. Recently, a pharmacoeconomic study found that the incorporation of EnteraGam into therapy delayed the use of biologics in a small cohort of patients.[43] Although the case series reported here suggest utility of this therapy, well-controlled studies are needed for EnteraGam in IBD.

EnteraGam is currently intended for the dietary management of chronic diarrhea and loose stools and must be administered under medical supervision. The incidence of adverse events in clinical studies is 2% to 5% in response to SBI. Since EnteraGam's introduction in 2013, it is estimated that nearly 3 million doses of product have been administered to more than 22,000 patients in the United States with an overall adverse event rate of less than 0.2%.[44] No serious adverse events have been attributed to EnteraGam during postmarketing surveillance or clinical studies. The most common adverse events reported by patients administered EnteraGam included mild nausea, constipation, headache, increased urination,

increased diarrhea, and joint pain. No interactions with food or drugs have been observed.

VSL#3

Probiotics have been used extensively in recent times for the management of gastrointestinal diseases such as traveler's diarrhea, infectious diarrhea (ie, *Clostridium difficile*), and constipation. Symptoms for IBS can vary greatly per patient but include diarrhea or constipation and abdominal pain, occasionally accompanied by bloating, flatulence, and incontinence. Although the pathogenesis of IBS is not known, anecdotal evidence in the clinical setting has suggested the use of probiotics as an adjunct modality for the management of constipation-predominant IBS (IBS-C) symptoms, not only for bloating but for the symptoms of abdominal pain and stool consistency as well. Clinical trials along with evidence-based data are still limited in quantity regarding the efficacy of probiotics in the management of gastrointestinal illnesses such as IBS-D. Therefore, many current studies focus on evaluating the efficacy of probiotics in these clinical settings.

VSL#3, a probiotic formulation specially formulated for IBS, UC, and ileal pouch disease, continues to show promise in managing these conditions. Unlike other probiotics, VSL#3 is a probiotic medical food that has a higher potency and consists of a greater number of probiotic bacteria, which includes 8 live probiotic strains. Studies have shown VSL#3 to be useful in managing a wide array of gastrointestinal conditions. One study involving 25 patients was designed to investigate the effect of VSL#3 on gastrointestinal transit and symptoms of IBS-D patients.[45] Patients were randomly assigned to receive VSL#3 or placebo for 8 weeks. No change occurred in gut transit time or satisfactory symptom management in IBS-D in patients on VSL#3 as compared to placebo; however, there was a statistically significant improvement in bloating for patients in the VSL#3 treatment arm. The study suggests further investigation on the effects of probiotics on IBS symptoms such as abdominal bloating. Although the physiology by which probiotics may improve abdominal bloating and flatulence is unknown, it is hypothesized that the decrease in gas-producing bacteria (ie, *C difficile*) may be a potential mechanism. Data have shown that a significant number of patients with IBS-D have reported abdominal bloating and flatulence as their most significant symptoms. Presently, there are no good medical alternatives for the management of abdominal bloating and flatulence, more commonly seen in patients with IBS-C. The small sample size of the study evaluating the efficacy of VSL#3 in IBS-D may have hindered the ability to detect statistically significant symptom improvement in the key symptoms associated with this condition, namely abdominal pain and diarrhea. More studies are needed to evaluate the type of IBS (constipation- or diarrhea-predominant) most suitable for probiotic therapy as well as the appropriate regimen and dosage for each subgroup.

It is important to note that the effectiveness of VSL#3 has also been evaluated in other disease states, such as pouchitis as a result of IBD. A minority of IBD patients (10%-20%) who have severe disease marked with either refractory inflammation or malignant mucosal changes may undergo surgical resection for definitive management. Restorative proctocolectomy with ileoanal pouch-anal anastomosis (IPAA) is commonly performed for UC patients with severe or refractory disease. During this procedure, the entire colon is removed and a reservoir for stool is constructed from the ileum and anastomosed to the anus. Although IPAA may provide long-term relief of symptoms in some IBD patients, other patients experience both short- and long-term complications. Pouchitis refers to nonspecific inflammation within the ileal reservoir leading to increased stool frequency, abdominal pain, and urgency. Most patients with pouchitis respond to antibiotic therapy. However, some patients can experience refractory or recurrent pouchitis. These patients may not respond to antibiotics or may have recurrent symptoms once therapy is stopped. Mimura and colleagues evaluated the efficacy of VSL#3 in maintaining remission after antibiotic therapy in patients with refractory pouchitis.[46] A total of 36 patients were randomized; 20 received VSL#3, and 16 received placebo. In the VSL#3 treatment arm, 17 patients (85%) achieved remission compared to 1 patient (6%) in the placebo arm. Although the exact mechanism by which VSL#3 is effective in patients with refractory or recurrent pouchitis is unknown, a potential hypothesis involves the effect of VSL#3 in decreasing intraluminal ileoanal pouch levels of TNFα and metalloproteinases. A study examining this question concluded that VSL#3 is effective as maintenance therapy in patients with recurrent or refractory pouchitis.[46] Another recently published study evaluated the efficacy of VSL#3 as an adjunctive therapy for UC with mesalamine and immunosuppressants.[47] The study found that VSL#3 in combination with these therapies improved the Ulcerative Colitis Disease Activity Index (UCDAI). A meta-analysis included 5 studies that identified a total of 441 patients.[48] The UCDAI was used to evaluate response and remission; 44.6% of patients on VSL#3 saw over 50% reduction in symptoms as compared to 25.1% in the placebo group. The meta-analysis concluded that when added to conventional therapy, VSL#3 was safe and more effective in achieving higher remission and response rates as compared to conventional therapy alone.

Additional studies have demonstrated efficacy for VSL#3 in nonrefractory IBD. Specifically, a double-blind,

placebo-controlled trial conducted by Tursi and colleagues randomized 144 patients to be treated with VSL#3 (n=71) for 8 weeks vs placebo (n=73).[49] The primary endpoint was the reduction of the UCDAI by 50% or more. The authors concluded that the study treatment was significantly superior to placebo in reducing the activity of mild to moderate UC. VSL#3 was also shown to improve rectal bleeding as well as potentially reinducing remission in relapsing UC patients. Of note, patients in both treatment arms were allowed to continue select alternative therapies such as mesalamine during the trial. A potential synergistic effect between VSL#3 and mesalamine was found. Although the exact interaction between the 2 therapies is unclear, it was proposed that VSL#3 either works in synergy with mesalamine or potentiates its anti-inflammatory effect. VSL#3 also was efficacious in improving the endoscopic appearance of colonic mucosa in the treated patients. It is important to note that although no major adverse events were seen in either treatment arm, the most appropriate VSL#3 dose for long-term maintenance therapy of UC requires further studies. The possibility of the development of bacteremia due to bacterial translocation should be considered in all patients receiving probiotics, especially in immunocompromised patients.[50]

Transitory bloating has been observed while patients adjust to VSL#3.[51] There is a theoretical risk of opportunistic infection with consumption of probiotics that contain lactobacilli,[52] and a few cases have been reported in the literature. There are no known food or drug interactions for VSL#3.

Modulen IBD

Modulen IBD is a whole-protein, powdered formulation for use as a sole nutrient source in the active phase of Crohn's disease, as well as a supplementary formula for the remission stage. Enteral nutrition has been studied in Crohn's disease for decades. The postulated benefits of enteral feeding as opposed to keeping patients nil per os or providing parenteral nutrition include attenuation of weight loss, decreased mucosal atrophy, and avoidance of line infections and malnutrition. Enteral nutrition is more common in the pediatric population, as parents are often opposed to using corticosteroids that can have negative effects on growth and development in young children. There have been fewer studies regarding the use of this formulation in UC, and further study is needed prior to recommending enteral nutrition for this form of IBD. The few studies that have been performed showed an increase in nutritional parameters such as albumin and prealbumin vs patients on total parenteral nutrition.[53,54]

Modulen IBD is calorie dense (1 kcal/mL), requiring less volume to be administered and theoretically requiring less work in digestion. In addition, the formula is rich in TGFβ, which is thought to decrease mucosal inflammation by attenuating the mucosal T-helper 1 cells that are active in Crohn's disease.[11,55] A study of various milk components in a mouse model of colitis compared Modulen IBD with iron-saturated lactoferrin, angiogenin, osteopontin, colostrum whey protein, and conjugated linoleic acid–enriched milk fat.[56] Effects on microscopic inflammation, angiogenesis, and clinical scores (including blood in stool) were measured. Modulen IBD was noted to be most effective at decreasing the clinical score at day 12 and was found to decrease angiogenesis.

The effects of 8 weeks of Modulen IBD on macroscopic and microscopic appearance as well as mucosal biologic markers were studied in 29 children with Crohn's disease.[57] Mucosal healing and clinical improvement were seen in 79% of the subjects. In addition, mucosal mRNA was measured for multiple IL proteins, IFN-γ, and TGFβ before and after the 8-week period. Decreased expression of IL-1β and IFN-γ mRNA (both proinflammatory), as well as increased expression of TGFβ mRNA (anti-inflammatory) were noted in the terminal ileum biopsies. This study described both a clinical and biologic response to Modulen IBD. Another study that analyzed amplified 16S rRNA from stool collected during treatment with Modulen IBD as a surrogate for intestinal flora found that possible changes in the microbiome may be responsible for disease remission in children with Crohn's disease.[58] The study included 9 children, 8 of whom had complete remission of their disease without requiring corticosteroids, measured using the Pediatric Crohn's Disease Activity Index (PCDAI). Electrophoresis of amplified 16S rRNA from stool samples was performed throughout the study with marked variation in the banding pattern noted in the subjects treated with exclusive enteral nutrition (EEN) vs healthy controls. In another study, Modulen IBD increased lean body mass in children receiving EEN (n=17) and improved concentration of micronutrients.[59] A study of 28 patients in Israel found an increase in body mass index in addition to a decrease in the PCDAI in patients receiving supplemental nutrition with Modulen IBD compared to those not receiving supplemental nutrition added to standard medical therapy.[60] A Spanish study also explored the efficacy of EEN using Modulen IBD.[61] The study outcomes were the PCDAI and fecal calprotectin levels over 8 weeks of treatment. Remission was achieved in 85% of patients by the end of 8 weeks.

Modulen IBD also appears to be beneficial for maintenance of Crohn's disease after achieving remission. A retrospective study of maintenance enteral nutrition (MEN) after EEN in 59 children during the first year after diagnosis with Crohn's disease was performed in the United Kingdom.[62] The patients were all given 8 weeks of EEN (either orally or via nasogastric tube), with 48 of

59 patients completing the 8 weeks of treatment. Fifteen patients continued MEN. Of these, 9 were taking concomitant azathioprine. A total of 93% of patients were in remission at 6 months and 60% at 12 months. Thirty-three patients did not continue MEN; of these, 20 were taking concomitant azathioprine. A total of 54% were in remission at 6 months and 45% at 12 months. These results suggest significant benefit with continued MEN.

A single case report utilizing Modulen IBD has been reported in an adult patient with IBD, with severe scleritis and psoriasis as extraintestinal manifestations of her Crohn's disease.[63] The patient was intolerant to azathioprine and was largely maintained on corticosteroids. She experienced temporary relief from infliximab (Remicade, Janssen) but eventually had diminishing returns and developed herpetic complications. She was started on an exclusive diet of Modulen IBD and achieved complete remission in 6 months, including resolution of her extraintestinal manifestations. A pilot study in adults suggested that Modulen IBD in addition to standard therapy may help to induce remission in the active phase of Crohn's disease.[64] Another study addressed maintenance of remission in adults comparing efficacy of Modulen IBD to mesalamine and suggests no difference in either arm (n=76).[19] These 2 studies were neither randomized nor placebo-controlled, and further studies are needed to assess the true efficacy of Modulen IBD in adults with Crohn's disease. Although exact mechanisms are unknown, the benefits of Modulen IBD are clear in pediatric patients with Crohn's disease and may be a valuable asset to help manage adults with Crohn's disease.

The manufacturer of Modulen IBD does not provide a listing of observed or potential adverse events, although there is a possibility for milk allergy as the product is isolated from milk.[65] In addition, long-term use of meal replacement with any enteral formula can lead to incomplete nutritional status in patients.

Vivonex

Vivonex is used for patients with severely impaired gastrointestinal function and is an elemental formulation of free amino acids with low levels of fat to help with gastric emptying and minimize pancreatic stimulation. It is available in 4 formulations with different caloric distributions: Vivonex T.E.N. contains 3% fat, Vivonex PLUS contains 6% fat, Vivonex RTF (tube feed only) contains 10% fat, and Vivonex Pediatric contains 25% fat. All formulations except Vivonex RTF can be used orally in addition to tube feeds.[10]

Vivonex has been studied extensively in the management of Crohn's disease. One study compared 2.1 L of Vivonex T.E.N. per day for 28 days (n=22) to 0.75 mg/kg of prednisolone for 14 days (n=20) followed by a taper.[66] The diet was not tolerated in 9 of the 22 patients in the enteral nutrition group. In addition, 3 patients deteriorated during the trial and required emergent treatment. Data were not included on the patients who did not complete their particular arm of the study. In patients who completed the trial, Vivonex T.E.N. was found to be as effective at inducing remission as prednisolone. The same study found that patients on an elemental diet relapsed more quickly than those in the prednisolone group. In another retrospective study, 16 patients with corticosteroid-refractory or -dependent Crohn's disease were treated with elemental diet (Vivonex).[67] Of the 16 patients, 10 were in remission at 4 weeks and off all medications, and 7 had a durable response at 6 months. This study suggests that not only can an elemental diet induce remission, but it can also lead to a sustained remission in some patients. Another study was performed in 21 patients treated for 4 weeks with elemental diet (n=11) vs corticosteroids (n=10), with 9 patients on the elemental diet and 8 patients on corticosteroids completing the study.[68] All of those who completed the study were in remission at the end of 4 weeks. Patients who did not complete the study were not included in the analysis. One study evaluated the efficacy of Vivonex on local complications, including perianal fistulas or ulceration, terminal ileal inflammation, bile salt diarrhea, skin breakdown near ostomy sites, and leakage, and found the formulation to be beneficial in all of these areas.[69] There have not been placebo-controlled, randomized trials of nutritional therapies yet in active Crohn's disease. Corticosteroids have been found to be more effective at inducing remission by a Cochrane systematic review.[70] Therefore, nutritional support should only be used in addition to standard medical therapies.

Burn victims have significant issues with gastrointestinal tract function, including decreased peristalsis, intestinal distention, possible ileus, decreased barrier function, decreased immune function, and ischemia leading to Curling (stress) ulcers.[71-73] Vivonex has been thought to reduce intestinal transit due to decreased fat content. An animal model of gastric emptying in burn victims showed that Vivonex was equivalent to control diet in gastric emptying; however, an oral rehydration solution was superior.[74] Another study evaluating changes in motility and translocation of bacteria in mice showed that Vivonex (as well as Ensure [Abott Laboratories] and Osmolite [Abott Laboratories]) did not change intestinal motility, but were associated with bacterial translocation to the mesenteric lymph nodes or liver.[75] This was thought to be due to significantly increased cecal bacterial overgrowth in the setting of increased enteral nutrition with suboptimal motility. According to these studies, it does not appear that Vivonex significantly changes intestinal motility in severely ill patients. A study comparing a high-carbohydrate and -protein diet (Vivonex) with a high-fat

diet (milk) in 940 children with severe burns (>40% of their total body surface area) showed a number of benefits in the Vivonex group.[76] The length of stay, rate of sepsis, hepatic steatosis, and organomegaly were all decreased in the Vivonex group. However, the effect on overall mortality was not significant. In a study comparing early enteral nutrition with Vivonex for 3 days followed by Ensure vs total parenteral nutrition in severe burn patients (n=82), a significant mortality benefit as well as a significantly more rapid recovery of immune function and normalization of cortisol and insulin levels were seen in the enteral nutrition group.[77] Enteral nutrition with Vivonex in burn patients also showed a decrease in gastrointestinal bleeding (20%) as compared to the usual diet consisting of a balanced meal with double portions and offered snacks (44%).[78] Major upper gastrointestinal bleeding and mortality have also been significantly decreased with Vivonex.

There are a number of other reported indications of Vivonex, some of which have been studied. Vivonex was evaluated in 6 patients with bile acid–induced diarrhea vs normal controls as well as nonbile acid–induced diarrhea.[79] A significant decrease was noted in the total fecal bile acid excretion, and improvements were noted in the number of bowel movements and urgency. Vivonex has been compared with other formulations in the treatment of malnutrition due to pancreatic insufficiency. One study compared Criticare HN (high nitrogen; Mead Johnson) to Vivonex HN and found both to increase blood urea nitrogen levels (a surrogate for protein absorption); however, Criticare HN led to more weight gain.[80] A small study comparing pancreatic secretory function in chronic pancreatitis when fasting with a regular diet and with an elemental diet (Vivonex HN) showed only minimal elevation in secretion with the elemental diet compared with fasting.[81] Vivonex has also been studied in an animal model of stressed mice.[82] The formulation was compared to 20 mg/kg and 60 mg/kg doses of cimetidine and an aluminum/magnesium antacid, and Vivonex was found to be superior. The mice were kept cold and restrained, which led to gastric lesions in all but the Vivonex-fed mice. Another study evaluated Vivonex in a group of patients with IBS and abnormal lactulose breath tests, and reported that 85% of the 93 remaining patients at the end of the study had normal breath tests after 3 weeks on an elemental diet.[83] IBS symptoms were also evaluated and noted to be improved. Another application of Vivonex is in allergy and immunology for atopic dermatitis and food allergy. Studies have shown both decreased levels of symptoms and decreased peripheral eosinophilia in patients on a diet composed solely of Vivonex.[84,85]

The manufacturer of Vivonex does not provide a listing of observed or potential adverse events. There are no known allergies to Vivonex, as it is a 100% free amino acid formula. Long-term use of meal replacement with any enteral formula can lead to incomplete nutritional status in patients.

Discussion

Over the past few years, medical foods have emerged as a tool for physicians to manage many gastrointestinal disorders, such as IBS, IBD, and HIV-associated enteropathy, as well as nongastrointestinal disorders. As illustrated in this paper, multiple animal and human studies have provided data purporting to show the efficacy of medical foods in managing multiple gastrointestinal and nongastrointestinal disorders. Many of these studies have followed open-label or retrospective case series formats, which are limited in their demonstration of efficacy. Although larger, well-controlled studies are needed to further assess efficacy in specific gastrointestinal conditions, the safety of these products may appeal to physicians who use therapy with diet and nutrition as part of their initial approach or for providers who have had failure with conventional therapies. Safe medical foods may be the initial step in managing various gastrointestinal disorders before moving to drugs with known and higher side-effect profiles. In addition, because the medical foods reviewed in this article do not have major food or drug interactions, they may be considered as add-on therapies in patients with more serious gastrointestinal conditions, as they can work alongside drugs in disease management to improve patient outcomes. More research will be needed to continue to evaluate medical food potential on patient care.

The authors gratefully acknowledge the review of Bruce Burnett, PhD, Vice President of Compliance, Regulatory & Medical Affairs of Entera Health Incorporated.

The authors have no relevant conflicts of interest to disclose.

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