

New therapeutic option for irritable bowel syndrome: Serum-derived bovine immunoglobulin

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well as other symptoms (*i.e.*, abdominal pain, bloating, and urgency) in patients with irritable bowel syndrome with diarrhea (IBS-D) and human immunodeficiency virus-associated enteropathy. This case series reports the outcomes of 14 IBS patients who received SBI as an addition to standard of care at an individual physician's clinical practice. The patients: 2 IBS with constipation (IBS-C), 7 IBS-D, 2 mixed diarrhea and constipation IBS (IBS-M) and 3 undefined IBS (IBS-U; also described by some physicians as IBS-Bloating), ranged in age from 22-87 years. SBI (5 g or 10 g daily dose) was added to the patient's current standard care and followed for several weeks to determine if symptoms were improved with the addition of SBI. Overall, 12 of the 14 patients indicated some level of improvement through direct questioning of the patients regarding changes from the prior visit. One IBS-Bloating patient had a resolution of symptoms and two patients (1 IBS-Bloating and 1 IBS-C) discontinued therapy because of insufficient relief. The 12 patients who continued on therapy reported an overall improvement in symptoms with better stool consistency, decreased frequency as well as reductions in abdominal pain, bloating, distention, and incontinence. In most cases, therapeutic effects of SBI were seen within the first four weeks of therapy with continued improvements at subsequent visits. SBI has a multifaceted mechanism of action and may help to manage IBS by providing a distinct protein source required to normalize bowel function, gastrointestinal microbiota, and nutritionally enhance tight junction protein expression between intestinal epithelial cells. SBI as a medical food provides a safe option for patients with IBS-D but may have application in other forms of IBS.

Abstract

Oral prescription medical foods have long been used in hospital settings but are also appropriate therapies for gastrointestinal disorders in outpatient medical practice. Oral serum-derived bovine immunoglobulin/protein isolate (SBI) has been shown in clinical studies to reduce loose stools and improve stool consistency as

Key words: Irritable bowel syndrome; Diarrhea; Immunoglobulin; Bovine; Serum-derived; Gastrointestinal disease; Medical food

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Core tip: Oral prescription medical foods are becoming part of the outpatient medical practice and are finding new uses as a therapeutic option for gastrointestinal disorders. This case series investigates the use of oral serum-derived bovine immunoglobulin/protein isolate (SBI) in the management of differing forms of irritable bowel syndrome (IBS). Because of the multifaceted mechanism of action, SBI provides a distinct protein source to normalize bowel function, gastrointestinal microbiota, and nutritionally enhance tight junction protein expression. As such, there may be potential use for patients with other forms of IBS besides IBS-D. Additional research is needed to explore this use.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder that is defined based upon the presence of abdominal pain and a change in bowel habit^[1,2]. It is further categorized based upon stool consistency leading to a diagnosis of IBS with either constipation (IBS-C), diarrhea (IBS-D), mixed with alternating constipation and diarrhea (IBS-M) or undefined (IBS-U), which may have symptoms of bloating and distention. Population-based studies have found IBS to be a common disorder affecting from 9%-22% of the population^[3,4].

IBS is the most commonly diagnosed gastrointestinal (GI) disorder and has both a detrimental impact on patient quality of life as well as affecting work productivity^[2,5,6]. When compared to another GI disorder like gastroesophageal reflux disease (GERD), IBS patients had significantly greater impairment in the ability to carry out daily activities of living and basic work activities, which led to a greater loss of work^[5,6]. IBS patients often suffer from other comorbidities such as anxiety, depression, fibromyalgia, migraine headaches, interstitial cystitis and temporomandibular joint syndrome^[2]. The impact from changes in quality of life and activities of daily living results in an estimated annual economic burden of \$25-50 billion^[2,5,6].

Successful management of IBS is dependent upon symptom relief but options tend to be limited. For those with IBS-D, the primary goal is to manage bowel symptoms (reduce stool frequency, urgency, and bloating; improve stool consistency), while managing abdominal symptoms (pain and discomfort). There is no single accepted therapy for IBS. While there are some limited evidence-based recommendations and guidelines, there is no general consensus among

clinicians for specific treatment options. Alosetron, a 5HT₃ antagonist, was originally approved for women with severe IBS-D because serotonin has been shown to affect motility and pain; however the safety profile has limited its use^[7,8]. Rifaximin is an oral antibiotic that has shown potential benefits for some IBS-D patients, and has been shown to reduce abdominal pain in patients with IBS^[9,10]. Other options include tricyclic antidepressants which can cause constipation, but can be of benefit improving stool consistency as well as addressing pain^[11]. Anti-diarrheals, like loperamide and diphenoxylate hydrochloride/atropine, can increase transit time thereby allowing for increased water absorption^[12]. Bulking agents such as methylcellulose and psyllium fiber also help with stool consistency^[13]. Low FODMAP (fermentable oligo-, di-, and monosaccharides and polyol sugars) diets are yet another option to help address discomfort, bloating and flatulence by minimizing the ingestion of certain sugars and vegetables^[14]. Despite the potential benefit of these various approaches, they all tend to provide limited improvements in patient symptoms leaving many patients unsatisfied with the overall effectiveness. As such, patients continue to seek other therapy options.

SBI (EnteraGam™) is a prescription medical food product intended for the clinical dietary management of intestinal disorders in patients with chronic loose and frequent stools who have a limited or impaired capacity to ingest, digest, absorb, or metabolize certain nutrients; it is used under physician supervision^[15]. SBI is a specially-formulated protein source consisting of > 90% protein, of which > 50% is immunoglobulin G (IgG)^[15]. Studies have demonstrated that SBI is safe and improves gastrointestinal symptoms (*e.g.*, chronic loose and frequent stools, abdominal discomfort, bloating, and urgency) in patients with IBS-D^[16] or HIV-associated enteropathy^[17]. Approximately 25%-50% of orally administered IgG survives digestion in the stomach and small intestine^[18]. The mechanism of action of SBI is postulated to involve binding to microbial components, maintaining immune balance in the gastrointestinal tract, managing gut barrier function including increasing expression of the tight junction proteins zonula occludens-1 (ZO1) and occludin, and improving nutrient uptake^[18]. As such, SBI may provide distinct nutrition in the form of immunoglobulins and other proteins for patients and physicians when conventional therapies fail to adequately manage IBS-D.

CASE REPORT

IBS has different clinical expressions based upon stool consistency or frequency, as well as other associated gastrointestinal symptoms. This retrospective chart analysis explores the use of SBI in the management of 14 IBS patients with differing forms: 7 IBS-D, 2 IBS-C, 2 IBS-M, and 3 IBS-Bloating (IBS-U) through clinical observations, physician questioning and patient

Table 1 Presentation of irritable bowel syndrome patients with diarrhea

Patient No./age (yr)/gender	Primary symptoms	Comorbidity	Other GI therapy	SBI therapy/duration	Outcome
IBS-D 1/24/M	Diarrhea, frequency urgency, ABD pain	Chronic urethritis ulcerative proctitis	Low FODMAP diet, mesalamine	Ongoing 32 wk	Complete resolution of symptoms
IBS-D 2/36/F	Diarrhea urgency incontinence	Hypothyroidism anxiety, depression	None	Ongoing 18 wk	Marked improvement in urgency and diarrhea
IBS-D 3/63/M	Diarrhea Flatulence, ABD cramps, urgency	Eosinophilic esophagitis, RHI, BPH	Pantoprazole	Ongoing 27 wk	Complete resolution of symptoms
IBS-D 4/86/M	Loose stools, urgency, cramping	COPD, lung cancer	Domperidone	Ongoing 12 wk	Marked improvement of urgency and diarrhea
IBS-D 5/36/F	Diarrhea, severe ABD pain	Ulcerative colitis	Low FODMAP diet, mesalamine	Ongoing 12 wk	No ABD pain, Loose stools/diarrhea improved
IBS-D 6/87/F	Diarrhea, ABD pain, distention, urgency	Osteoporosis, GERD, anxiety	Perphenazine/amitriptyline, omeprazole	Ongoing 17 wk	Dramatic reduction in symptoms
IBS-D 7/66/M	Diarrhea, urgency, incontinenc, ABD pain	Hypertension, benign prostatic hyperplasia	Tramadol	Ongoing 16 wk	Marked reduction in pain and urgency, Formed bowel movements

ABD: Abdominal; IBS-D: Irritable bowel syndrome with diarrhea; SBI: Serum-derived bovine immunoglobulin; GI: Gastrointestinal; GERD: Gastroesophageal reflux disease.

Table 2 Presentation of irritable bowel syndrome patients with constipation

Patient No./age (yr)/gender	Primary symptoms	Comorbidity	Other GI therapy	SBI therapy/duration	Outcome
IBS-C 1/22/F	Constipation, bloating, distension	None	Low FODMAP diet, linaclotide, lubiprostone	Discontinued after 11 wk	Ineffective
IBS-C 2/55/F	Bloating, distension, nausea, obstipation	Non-erosive reflux disease	lubiprostone	Ongoing 14 wk	Reduced bloating and distension, obstipation unchanged

IBS-C: Irritable bowel syndrome with constipation; SBI: Serum-derived bovine immunoglobulin; GI: Gastrointestinal.

reporting.

The first group investigated were those patients with IBS-D (Table 1). Overall these patients, ranging in from 24-87 years of age, responded well to SBI therapy and all continued usage. The key complaints among these 7 patients were diarrhea (6), urgency (6), abdominal pain (6), frequency (5), and incontinence but symptoms of flatulence, distension, and cramping were also noted by some patients. While symptoms varied among these patients, the general response indicated a consistent improvement in abdominal and bowel symptoms with a marked reduction in abdominal pain, diarrhea, urgency and an improved stool consistency. There was also a noted resolution of incontinence. The duration of SBI therapy ranged from 17-32 wk and all patients continue their SBI therapy for management of their IBS-D symptoms.

The second group investigated consisted of two

patients diagnosed with IBS-C (Table 2). While SBI is specifically intended for use in IBS-D rather than IBS-C, the potential mechanism of action regarding barrier restoration may provide some symptom management in IBS-C. For one patient, a 22 year old female, SBI was ineffective in managing the patient's overall IBS-C symptoms. In a second 55 year female patient, SBI improved the patient's bloating, distension and nausea. However, the patient had no improvement in her obstipation (severe constipation resulting from an intestinal obstruction). The benefits perceived by the patient, however, were subjectively sufficient during the 14 wk of SBI therapy that the patient has elected to continue the therapy.

The third group was two patients experiencing alternating diarrhea and constipation symptoms noted as IBS-M (Table 3). For the 33 year old female patient, there was an overall improvement in IBS-M

Table 3 Presentation of irritable bowel syndrome patients with mixed with alternating constipation and diarrhea

Patient No./age (yr)/gender	Primary Symptoms	Comorbidity	Other GI Therapy	SBI Therapy/Duration	Outcome
IBS-M 1/33/F	Alternating diarrhea and constipation, bloating, distension, ABD pain	Morbid obesity	Low FODMAP diet	Ongoing 15 wk	Overall improvement, mild obstipation, reduced bloating
IBS-M 2/66/F	Alternating diarrhea and constipation, bloating, distension	Osteoporosis	Low FODMAP diet	Ongoing 14 wk	No bloating or distension, improved bowel movements

IBS-M: Irritable bowel syndrome with mixed with alternating constipation and diarrhea; SBI: Serum-derived bovine immunoglobulin; GI: Gastrointestinal.

Table 4 Presentation of patients with irritable bowel syndrome -bloating

Patient No./age (yr)/gender	Primary symptoms	Comorbidity	Other GI therapy	SBI therapy/duration	Outcome
IBS-U 1/50/M	Gas, Bloating, ABD Pain	GERD, osteoarthritis	polycarbophil, saccharomyces boulardii lyo, polyethylene glycol 3350, prn	Ongoing 35 wk	Resolution of symptoms
IBS-U 2/82/F	Severe ABD pain, bloating, distension	Hypertension, atherosclerotic cardiovascular disease	Antidiarrheals	Discontinued after 6 wk	Unimproved
IBS-U 3/62/F	Bloating, distension, ABD pain, flatulence	Osteoporosis	denosumab, rifaximin, Low FODMAP diet	Completed after 8 wk	Resolution of symptoms

IBS-Bloating: Irritable bowel syndrome with bloating; SBI: Serum-derived bovine immunoglobulin; GI: Gastrointestinal; GERD: Gastroesophageal reflux disease.

and a reduction in bloating during the 15 wk of SBI therapy although mild obstipation was noted. In a second patient, 66 years old female, there was an elimination of the patient’s bloating and distension and improvement in the bowel movements during the 14 wk of SBI therapy. Both patients are on low FODMAP diets and continue their SBI therapy.

The final group of IBS patients was those with no specific bowel symptoms associated with stool consistency, but who indicated that their primary IBS symptom was bloating (Table 4). For this group of patients, an 82 year female patient discontinued SBI therapy after 6 wk indicating there was insufficient relief of symptoms. A second patient, a 62 years old female, completed 8 wk of SBI therapy and indicated a resolution of her gastrointestinal symptoms (bloating, distension, flatulence, and abdominal pain) but given the cyclic nature of IBS, it is possible that these symptoms may recur. A third patient, a 50 years old male whose primary symptoms included gas, bloating and abdominal pain, reported a resolution of symptoms. He has been managed with SBI therapy for 35 wk and continues on therapy.

No adverse effects have been noted due to SBI therapy in any of the IBS patient populations being managed with the product.

DISCUSSION

For patients with IBS-D observed in this physician’s clinical practice, SBI has been highly effective in managing

chronic loose and frequent stools in IBS. For patients with IBS-C, the results are inconclusive due to small sample size but seem less effective in this patient population. For patients with IBS-M, there is some potential for efficacy during bouts of diarrhea and reduction in bloating but the full extent of benefit suggests some mixed results. Because of the alternating nature of symptoms in IBS-M patients, this population is often difficult to manage. Further investigation is warranted to determine the potential timing and management of dosing in this patient population. Similarly for patients with IBS-bloating, there appears to be some alleviation in bloating symptoms but the full extent of the benefit is mixed. Additional study may help determine the extent of benefit that is possible in this population. Despite these findings, the results and conclusions drawn from these patients must be tempered by the small sample sizes.

While the findings in patients with IBS-D were expected based upon prior clinical evidence^[16], the elements of benefit for patients with other types of IBS, particularly for IBS-M and IBS-bloating, merit more study. Such investigations will provide for more thorough analysis of SBI-mediated outcomes in these types of IBS patients. While patients with IBS-C share some common symptoms with other IBS patients, the results in patients with IBS-C were inconclusive and more data is needed to draw any final conclusions.

SBI is intended specifically for the management of intestinal disorders in patients with chronic loose and frequent stools, such conditions as IBS-D and HIV-

associated enteropathy under physician supervision^[15]. These findings suggest improvements in symptoms that affect patients with IBS-D and other types of IBS without any adverse effects. This further supports the SBI designation as Generally Recognized As Safe (GRAS) or food-like safety, an FDA requirement for this category of therapeutics^[15]. As such, SBI as a medical food would appear to have safe and practical applications in the management of IBS (particularly patients with IBS-D) and further investigation is needed to determine the extent of benefits that SBI holds for patients with other forms of IBS.

COMMENTS

Case characteristics

This case series reports the outcomes of 14 irritable bowel syndrome (IBS) patients (2 IBS-C, 7 IBS-D, 2 IBS-M and 3 IBS-Bloating), ages 22-87 years, who received serum-derived bovine immunoglobulin/protein isolate (SBI) as an addition to standard of care in a clinical practice setting.

Clinical diagnosis

General diagnosis consisted of abdominal pain with altered bowel habits associated with diarrhea and/or constipation or bloating.

Differential diagnosis

Irritable bowel syndrome with diarrhea, constipation, mixed (diarrhea and constipation) or bloating.

Laboratory diagnosis

Individual laboratory testing was not provided as patients had an established diagnosis of IBS.

Imaging diagnosis

Imaging such as a colonoscopy was not provided as patients had an established diagnosis of IBS.

Pathological diagnosis

Pathological diagnosis was not provided as patients had an established diagnosis of IBS.

Treatment

Serum-derived bovine (SBI) immunoglobulin/protein isolate (5 g or 10 g/d) was added to the patients' current standard care and followed for several weeks to determine if symptoms improved.

Related reports

Despite some limited evidence based recommendations for treatment of IBS, there is no clear consensus on therapeutic options for IBS and patients are often dissatisfied with their current therapeutic options.

Term explanation

IBS-bloating or IBS-U refers to patients without any distinctive stool consistency patterns for diagnosis as IBS-D, IBS-C or IBS-M but show symptoms of IBS such as abdominal pain with a chief complaint of bloating rather than stool consistency.

Experiences and lessons

Overall, 12 of the 14 IBS patients using SBI indicated some level of improvement with onset within the first four weeks of therapy and 11 of the 14 are continuing therapy, but two patients discontinued therapy because of insufficient relief.

Peer-review

The article describes 14 cases of IBS where SBI was added to current standard of care and found improvement in 12 cases. The article highlights the potential benefits that can come from a medical food like SBI in a clinical practice and the data suggest the need for further study to confirm these practice findings.

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