Case Series Investigating the Clinical Practice Experience of Serum-Derived Bovine Immunoglobulin/Protein Isolate (SBI) in the Clinical Management of Patients with Inflammatory Bowel Disease

Larry Good1 and Raymond Panas2

1South Nassau Communities Hospital, Oceanside, NY, USA
2Entera Health, Inc., Medical Affairs, Cary, NC, USA

Corresponding author: Larry Good, MD, 444 Merrick Rd, Lynbrook, NY 11563, USA, Tel: (516) 766-0300; Fax: (516) 766-2444; E-mail: good1b@optonline.com

Rec date: Feb 19, 2015, Acc date: Mar 20, 2015, Pub date: Mar 27, 2015

Abstract

Background: Serum-derived bovine immunoglobulin/protein isolate (SBI), a specially formulated oral protein source of >50% IgG and ~60% total immunoglobulins, has a multifaceted mechanism of action binding microbial components, maintaining gastrointestinal immune balance, managing gut barrier function and improving nutrient utilization. IBD animal models and a human refractory case study demonstrated that SBI can attenuate both inflammatory biomarkers and histological parameters in the bowel. Additionally, SBI is intended for the clinical dietary management of intestinal disorders due to limited/impaired capacity to ingest, digest, absorb or metabolize certain nutrients/foodstuffs or clinical dietary management of chronic loose and frequent stools. Given the known efficacy of SBI in gastrointestinal disorders and effects demonstrated in IBD animal models, SBI may help in the nutritional management of Inflammatory Bowel Disease (IBD) patients.

Methods: In a clinical practice setting, we retrospectively evaluated seven ulcerative colitis (UC) and Crohn’s disease (CD) patients who incorporated SBI into their therapeutic regimens. All patients previously failed to adequately respond to conventional drug therapies. Their SBI response was assessed to determine its effect on further management in IBD patients.

Results: The addition of SBI for nutritional management resulted in improved IBD symptoms including chronic loose and frequent stools. The UC patients reported resolution of symptoms such as rectal bleeding, urgency, and/or nocturnal incontinence. The CD patients reported weight improvements, other therapy reductions, and/or decrease ileostomy output and creatinine levels.

Conclusion: Although this was a retrospective assessment of a small case series, the evidence suggests that SBI provided further management of IBD patients who were not fully controlled on traditional therapies by providing for distinctive nutritional requirements in these patients. Further study is warranted to evaluate this option as part of IBD therapy.

Keywords: Inflammatory bowel disease; Diarrhea; Immunoglobulin; Crohn’s disease; Ulcerative colitis; Bovine; Medical food

Background

Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition resulting from an immune dysregulation of the intestinal tract, the cause of which remains to be determined [1]. This dysregulation results in two distinct disease states: ulcerative colitis (UC) and Crohn’s disease (CD). Ulcerative colitis is a disease of unknown etiology that produces chronic inflammation of the colon, whereas CD is relapsing inflammatory condition affecting any part of the gastrointestinal tract. As a colonic inflammatory bowel disorder, patients with UC often present with symptoms of bloody loose stools, abdominal cramps, and fatigue [2], while patients with CD frequently present with symptoms of abdominal pain, fever, and clinical signs of bowel obstruction or bloody loose stools or mucus [3]. In the US alone, it is estimated that IBD affects more than 1.6 million individuals [4].

While there may be many factors that contribute to IBD, current treatment methods target the clinical symptoms associated with the inflammatory and immune responses [1]. Commonly, these consist of various pharmaceutical agents such as 5-aminosalicylic acid, corticosteroids, immunosuppressents and immunomodulators [5]. Biologics are the newest option for IBD treatment and work by targeting and suppressing TNF-α or by binding to integrin α4β7 in order to reduce inflammation [6,7]. However, some patients have been found to develop antibodies to anti-TNF biological agents and lose response to the treatment [6]. Although no specific organism has been linked with IBD, it has been shown that IBD patients lack diversity in gut microbiota [8,9] and have a disruption of the intestinal barrier [10]. Thus, antibiotics have also been used to manage IBD in an effort to reduce intestinal bacteria and to suppress the gastrointestinal immune response [11].

All of these various therapeutic options are used in an effort to avoid the need for surgery and address complications associated with IBD. Since there is no cure for IBD, current treatment goals according to the Crohn’s and Colitis Foundation of America are to induce
remission, maintain remission by preventing flare-ups, and improve overall quality of life [11]. For a patient being treated with UC, 70% with active disease are likely to relapse with another flare within the following year while 30% in remission are likely to relapse within the following year. For patients being treated for CD, about 20% in remission will relapse within one year [4]. On average in any given year, about 48% of patients with UC and 45% of CD patients will be in remission [4].

Other therapeutic approaches are still needed to manage IBD and achieve greater stability in the overall remission of this condition. Furthermore, by controlling inflammation, the intestines can properly absorb essential nutrients [11], which can further enhance the well-being and maintenance of IBD patients. Serum-derived bovine immunoglobulin/protein isolate (SBI) was considered for therapy in CD and UC patients in this practice due to positive results in management of chronic loose and frequent stools in a variety of GI conditions [12-14] as well as in animal models [15,16] and a human case study of UC [17]. Based on the results presented herein, SBI may be a nutritional add-on therapy which can provide distinct nutrition unique for further management in IBD.

Methods

This is a retrospective case series of seven patients with IBD: 3 patients with UC and 4 patients with CD. No formal inclusion or exclusion criteria were used in the assessment of these particular cases but rather the fact that patients were refractory to standard IBD therapy and provided SBI therapy as part of therapeutic regimen. Given the ability of SBI to manage chronic loose and frequent stools in other gastrointestinal conditions [12-17], it was considered as a therapeutic option for the management of IBD patients who often experience similar symptoms. Additionally, due to the proposed mechanism of action of SBI [18] and animal models in IBD [15,16], it was reasoned that SBI might also restore a homeostatic immune balance which may enhance management of UC and CD. SBI was utilized as part of a standard-of-care nutritional approach for the management of each patient’s condition reported here and their individual response to the SBI addition to therapy was assessed.

Serum-derived Bovine Immunoglobulin/Protein Isolate

Serum-derived bovine immunoglobulin/protein isolate (SBI) is a prescription medical food product intended to provide for the distinctive nutritional requirements unique for the clinical dietary management of specific intestinal disorders [e.g., irritable bowel syndrome with diarrhea (IBS-D), inflammatory bowel disease (IBD) and HIV-associated enteropathy] under physician supervision [19]. SBI, as an oral protein source with >50% IgG, 1% IgA and 5% IgM as well as other serum proteins, has a multifaceted mechanism of action (Figure 1) which includes binding to microbial components within the intestinal tract, sterically preventing the penetration of antigens through damaged epithelial cell tight junctions and normalizing immune response due to steric and immune exclusion [18,20]. This has downstream effects which include both the maintenance of GI immune balance and management of gut barrier function resulting in improved nutrient utilization [18].

![Figure 1: Mechanism of action of serum-derived bovine Immunoglobulin.](image)

Case Presentations and Results

Ulcerative colitis

A 66-year-old Caucasian female (Patient 1) has a history of hypertension, hyperlipidemia, and obesity (weight 213.8 lbs.). Prior medications were reported to include atorvastatin and metoprolol. The patient presented with 10-12 watery bowel movements/day for 6 weeks. Additionally, the patient reported urgency, nocturnal diarrhea (loose/watery stools) and some GI bleeding. CT scan indicated diffuse colitis and a Prometheus® IBD sgi Diagnostic™ (San Diego, CA) test was positive for UC. The patient’s stool cultures were negative. A colonoscopy confirmed pan colitis with crypt abscess and inflammation. Standard therapy with budesonide and mesalamine for 14 days did not improve the patients’ symptoms. The budesonide was discontinued and SBI at 5 g/day was added to the mesalamine treatment regimen for nutritional support. After nearly 3 weeks, the patient reported an improvement in gastrointestinal symptoms with a reduction in bowel movements to 3-6 soft bowel movements/day with no further rectal bleeding. SBI therapy was continued at 5 g/day along with mesalamine and by the end of 4 weeks of therapy, the bowel movements were further reduced to 3-4 formed stools/day with no associated symptoms. The patient has continued to use of SBI at 5 g/day along with mesalamine without any associated symptoms for nearly 6 months. Given the stable management of the condition with the addition of SBI to the mesalamine therapy, no further changes in therapy are planned.

A 55-year-old Caucasian male (Patient 2) has a history of UC since 2001 which led to a proctocolectomy and an ileoanal anastomosis (J-Pouch). The patient’s medical history included benign prostatic hyperplasia, Parkinson’s disease and chronic intermittent pouchitis. His medications included carbidopa-levodopa, Saccharomyces boulardii probiotic, and tamsulosin. The patient’s pouchitis has
presented for over 10 years as intermittent episodes of 10-12 loose bowel movements/day along with urgency, bleeding and mucous discharge. The pouchitis was recently exacerbated but conventional therapy of budesonide and ciprofloxacin for 14 days that failed to improve his condition and a pouchoscopy revealed no new findings. Although pouchitis can resolve spontaneously, many patients have frequent recurrent episodes. The patient was given SBI 5 g/day as monotherapy because of the aforementioned mechanism of action for SBI. At the 6 week follow-up visit, the patient reported no diarrhea (loose or watery stools), urgency, blood or mucous in his stools. The patient has maintained SBI 5 g/day therapy for nearly 6 months without any exacerbations of the pouchitis. As such, this is the longest period of time that the patient has remained without symptomatic pouchitis.

A 24-year-old Caucasian male (Patient 3) presented with loose/ water bowel movements and rectal bleeding. There was no medical history or recent medication suggestive of any specific issues. A flexible sigmoidoscopy was performed and indicated a Mayo Grade 3 ulcerative proctitis. The patient was treated with mesalamine suppositories and SBI 5 g/day for 14 days. At the follow-up exam, no diarrhea (loose/water stools) or rectal blood was noted. The mesalamine suppositories were discontinued but the patient was continued on the SBI therapy at 5 g/day. At 3 months of SBI therapy, the patient remained asymptomatic. Because the patient was well-managed, no follow up sigmoidoscopy was performed. The patient continues to be asymptomatic and has remained on SBI therapy at 5 g/day for approximately 9 months.

**Crohn’s Disease**

A 53-year-old Caucasian male (Patient 4) has a history of CD for more than 30 years. The patient has an established Brooke ileostomy and subsequent small bowel resection leaving approximately 150 cm of small bowel. The patient’s complex medical history includes chronic dehydration, short bowel syndrome, nephrolithiasis, and hypomagnesemia requiring routine IM replacement with magnesium sulfate. Additionally, the patient reported chronic pain due to peripheral neuropathy. His medications include 6-mercaptopurine, fentanyl patch, alprazolam, and omeprazole. Because of concerns regarding his chronic dehydration and high ileostomy output (5 litres/day), a small bowel series was performed revealing a minimal terminal ileitis. SBI 5 g/day was initiated into his therapy regimen with improvements beginning to be seen within 4 weeks. After approximately 10 weeks ileostomy output was reduced from 3.5 liters to 1.2 liters/day and remained consistent while on SBI therapy. Laboratory results at 5 months noted further improvement in creatinine levels from 3.2 to 2.9 mg/dL with further reduction to 2.6 mg/dL after the end of 9 months of therapy. At the end of 7 months of SBI therapy, the patient had an infusaport installed and now receives magnesium sulfate one to two times per month. Given these overall beneficial outcomes, the patient has remained on SBI therapy at 5 g/day for over 9 months and continues this therapy along with his other medications.

A 54-year-old Caucasian male (Patient 5) has a history of CD and a right hemicolecotomy for nearly 20 years. The patient failed to respond to infliximab or adalimumab therapy, resulting in intermittent steroid use to manage his symptoms. An MR Enterography noted active small bowel disease which is indicative of his flares with abdominal pain, cramps and diarrhea (loose/watery stools). SBI 5 g BID was incorporated into the patient’s therapy, resulting in a resolution of his abdominal pain and cramps in about 2 weeks. After 3 months, this allowed for a successful taper off of the steroid therapy and replaced with vedolizumab for maintenance therapy without the return of symptoms. The patient has remained on a maintenance dose of SBI 5 g BID and vedolizumab to manage his condition for nearly 8 months.

**Discussion**

SBI, as a specially formulated product of enriched immunoglobulins, may work through several different mechanisms including binding microbial components. SBI may help foster a stable microbiota allowing for the establishment of a homeostatic immune environment in the intestine to further manage gut barrier function and promote increased nutrient metabolism and utilization [13,15,16,18-20]. Clinically, SBI has been utilized for the management of chronic loose and frequent stools in IBS-D [12], HIV-enteropathy [13], chronic mesenteric ischemia [14] and short bowel syndrome [21]. There is both animal and human evidence that suggests that SBI may be appropriate for use in IBD patients. In an animal model using altered Schaedler flora mice, dextran sulphate sodium (DSS) was used to induce colitis [16]. The addition of SBI attenuated “DSS induced” inflammation in the cecum and colon compared to the control mice. Serum biomarkers for gut inflammation were significantly lower in DSS-induced mice treated with SBI which was correlated through histological measures [16]. This DDS mouse model demonstrated the ability of SBI to minimize the inflammatory affects that can be seen in both CD and UC. A second animal model using wild type and knockout (KO) mdrla mice, SBI was able to block colon crypt permeability and significantly reduce inflammatory markers (TNF-α, IFN-γ and iNOS RNA expression) which also correlated to a significant reduction in goblet cells and MUC 2 and TFF3 expression in the KO mice [15]. The dietary inclusion of SBI in this IBD model further demonstrated a potential of SBI to restore colonic barrier function. In a refractory UC patient who discontinued adalimumab due to septic arthritis infection after surgery, SBI was able to decrease daily watery stools from 10-15 to 1-2 normal stools after one month of therapy [17]. Additionally,
there were noted improvements in serum laboratory findings (albumin, erythrocyte sedimentation rate, and white blood cell count) as well as endoscopic evidence of a normalized colonic mucosa [17].

Given the known human efficacy of SBI in several diverse GI conditions and the potential efficacy noted in IBD animal models, SBI may have a practical application in the dietary management of CD and UC.

In this retrospective review of several clinical cases presented herein, patients had experienced episodes of chronic loose and frequent stools as a result of their IBD, even while on traditional drug therapies, and began to see improvement within 2 weeks after addition of SBI administration. For two of the three UC patients, there was a complete resolution of their loose and watery stools; one patient had a significant reduction in bowel movements from 10-12 soft stools/day to 3-4 formed stools/day. All three patients additionally reported a resolution of their rectal bleeding, while two patients reported a complete reduction of urgency and one patient reported that nocturnal incontinence episodes had ceased. For Patient 2, there was also no further exacerbation of the pouchitis.

For those patients with CD, they too reported an overall improvement in their CD symptoms during the management of their disease when SBI was included. Patient 4 had a decrease in both the ileostomy output and creatinine levels while Patient 6 was able to increase his weight by approximately 10 pounds (6.3%; BMI=24.1) as a result of the resolution of his loose, watery stools and presumably increased nutrient uptake and utilization. Patients 5 and 7 were able to modify their CD treatment: Patient 5 was able to reduce his adalimumab injections from weekly to biweekly events and Patient 7 was able to successfully taper off steroid therapy given the resolution of his abdominal pain and cramps. Reductions in drug therapies, especially steroids reduces the chance of side effects associated with long-term use, and for biologics can lead to cost savings for the patient and healthcare system.

All seven of the IBD patients presented here had treated with conventional drug therapy related to their condition and failed to adequately respond. The initiation of SBI at 5 g once or twice daily resulted in a significant management of their conditions starting in about 2 weeks. The ongoing use of SBI therapy has helped in the continued management of the patients’ chronic condition for up to 15 months without reported side effects. Given the overall improvements in response seen by these patients, long-term therapy will continue to long-term use, and for biologics can lead to cost savings for the patient and healthcare system.

Endoscopic and histological remission would be valuable to further assess the specific effect of SBI. However, endoscopic procedures and biopsies are not routinely performed on patients in clinical practice settings when patients’ are being adequately managed, lacking exacerbation of their condition, or lacking warning signs that may warrant further endoscopic evaluation. As such, this data is understandably lacking in the presented patients. Additionally, as patients were not removed from other conventional therapies, it is difficult to assess if SBI alone contributed to maintenance of homeostatic immune balance. While it is important to note that spontaneous remissions and exacerbations can occur in IBD, for these patients the addition of SBI enhanced the management of their overall IBD condition by providing distinctive nutrition required in these patients to assist in bringing their disease into a state of clinical remission, an outcome that was not achieved through conventional therapies alone.

### Conclusion

While this report is limited by a small sample size as well as lack of well-controlled research design, these clinical practice cases nonetheless demonstrate that SBI can have an impact on management of chronic loose and frequent stools associated with IBD. Recognizing the potential mechanism of action of SBI along with the clinical observations from these patients for as long as 15 months, SBI may have a practical application as part of the clinical dietary management of IBD. Since these patients have normal diets containing adequate protein content, specially formulated SBI administered at 5 to 10 g of additional protein per day may provide for a distinctive nutritional requirement to support the clinical management of these patients’ unique conditions. These clinical observations provide case evidence and justification for additional research to fully understand the utility of this therapeutic medical food in the nutritional management of IBD as well as the application of SBI in the long-term health and management of these patients.

### References

1. Levesque BG, Sandborn WJ, Ruel J, Feagan BG, Sands BE, et al. (2015) Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. Gastroenterology 148: 37-51.
2. (2014) Crohn’s and Colitis Foundation of America. The facts about inflammatory bowel disease I-20.
3. Danese S, Fiocchi C (2011) Ulcerative colitis. N Engl J Med 365: 1713-1725.
4. Baumgart DC, Sandborn WJ (2012) Crohn’s disease. Lancet 380: 1590-1605.
5. Engel MA, Neurath MF (2010) New pathophysiological insights and modern treatment of IBD. J Gastroenterol 45: 571-583.
6. Moss AC, Brinks V, Carpenter JF (2013) Review article: immunogenicity of anti-TNF biologics in IBD - the role of patient, product and prescriber factors. Aliment Pharmacol Ther 38: 1188-1197.
7. Solem D, Chapman T, Yang LL, Wyatt T, Egan R, et al. (2009) The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. J Pharmacol Exp Ther 330: 864-875.
8. Legape P, Häslar R, Spehlmann ME, Rehman A, Zvirbliene A, et al. (2011) Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. Gastroenterology 141: 227-236.
9. Moussata D, Goetz M, Gloeckner A, Kerner M, Campbell B, et al. (2011) Confocal laser endomicroscopy is a new imaging modality for recognition of intramucosal bacteria in inflammatory bowel disease in vivo. Gut 60: 26-33.
10. Zeissig S, Bürgel N, Günzel D, Richter J, Mankertz J, et al. (2007) Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn’s disease. Gut 56: 61-72.
11. (2014) Crohn’s and Colitis Foundation of America. Treatment for IBD [CCFA Website].
12. Wilson D, Evans M, Weaver E, Shaw AL, Klein GI. (2012) Evaluation of serum-derived bovine immunoglobulin protein isolate in subjects with diarrhea-predominant irritable bowel syndrome. Clin Med Insights Gastroenterol 6: 49-60.
13. Asmuth DM, Ma ZM, Albanese A, Sandler NG, Devaraj S, et al. (2013) Oral Serum-Derived Bovine. Immunoglobulin Improves Duodenal Immune Reconstitution and Absorption Function in Patients with HIV Enteropathy. AIDS 27: 2207-2217.
14. Good L, Burnett BP (2015) Management of Loose, Frequent Stools and Fecal Incontinence in a Chronic Mesenteric Ischemia Patient with Oral Serum-derived Bovine Immunoglobulin. Clin Med Insights Gastroenterol 8: 7-11.
15. Moret AM, Mira L, Maija M (2009) Dietary spray-dried plasma protein supplements attenuate the changes in colitis markers in the Modulator mouse model of colitis. Gastroenterol. 136: A771.

16. Maas KJ, Brand MW, Henderson A (2014) Serum-derived bovine immunoglobulin/protein isolate attenuated DSS-induced colitis in a defined floral model. Gastroenterol 146: S641.

17. Dryden GW, Jasion VS (2014) Use of serum-derived bovine immunoglobulin/protein isolate (SBI) to manage refractory ulcerative colitis symptoms and avoid surgery. Presented at 2014 Annual Meeting American College of Gastroenterology (ACG), October 17-22, 2014, Philadelphia, PA.

18. Petschow BW, Burnett B, Shaw AL, Weaver EM1, Klein GL1 (2014) Serum-derived bovine immunoglobulin/protein isolate: postulated mechanism of action for management of enteropathy. Clin Exp Gastroenterol 7: 181-190.

19. (2015) Entera Health, Inc. EnteraGam Package Insert, February.

20. Detzel CJ, Horgan A, Henderson AL (2014) Development of a co-culture model of the intestinal epithelium to study barrier function and immune exclusion by bovine IgG. Presented at the 2014 ASPEN Annual Meeting, January 18-21, 2014, Savannah, GA.

21. Hilal RE (2014) A case of short bowel syndrome managed with a prescription medical food product, serum-derived bovine immunoglobulin/protein isolate (SBI). Presented at 2014 Annual Meeting American College of Gastroenterology (ACG), October 17-22, 2014, Philadelphia, PA.