Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin

Ira Shafran, Patricia Burgunder, David Wei, Hayley E. Young, Gerald Klein and Bruce P. Burnett

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Abstract

Introduction: The clinical effect of oral serum-derived bovine immunoglobulin/protein isolate (SBI) on symptom and disease management in patients with inflammatory bowel disease (IBD) is reported in this retrospective case series.

Methods: A single-center, retrospective chart review of IBD patients [$N = 45$; Crohn's disease (CD), $n = 38$ and ulcerative colitis (UC), $n = 7$] with limited to no response to traditional pharmaceutical therapies in controlling symptoms was performed after providing SBI (5 g/day) for nutritional support. Patients were contacted at least monthly to assess response to SBI for symptom management measured by a Likert scale (0 = none; 1 = minimal; 2 = moderate; 3 = significant; 4 = complete). Analysis of variance (ANOVA) was performed on response to therapy based on patient characteristics (age, gender, race) and IBD diagnosis. A multivariate ordered logistical regression model was performed to determine the odds ratio in overall disease management between week 1 and week 12. Finally, the overall group response and percent improvement to SBI was determined over 12 weeks.

Results: The odds ratio from the regression model demonstrated that IBD patients were 2.8 times more likely to report clinical improvement in symptom scores with the addition of SBI to their therapeutic regimens [95% confidence interval (CI) 1.266–6.016, $p = 0.011$]. Disease management was not significantly associated with age, gender, race or disease state. The percentage of patients reporting a response to SBI therapy at week 1 was 49% which increased to 76% after 12 weeks with the fraction of responders gaining significant symptom improvement doubling during the same time period (9% versus 20%). Overall, this group of IBD patients showed increased, steady response to SBI therapy between week 1 and 12 with no reported side effects.

Conclusion: These results suggest that SBI improves clinical management of IBD patients who are not fully managed on traditional therapies. SBI should be considered for the nutritional support of IBD regardless of disease activity, location, phenotype, duration, or complexity.

Keywords: Crohn's disease, inflammatory bowel disease, oral immunoglobulin, serum-derived bovine immunoglobulin/protein isolate, ulcerative colitis

Introduction

Chronic inflammation of all or part of the intestinal tract is the defining characteristic for inflammatory bowel disease (IBD). Crohn's disease (CD) and ulcerative colitis (UC) are the two major disease states of IBD, although microscopic colitis is also sometimes included [Danese and Fiocchi, 2011; Baumgart and Sandborn, 2012]. Crohn's disease is a relapsing, chronic, systemic,

transmural inflammatory disease which can involve the entire gastrointestinal (GI) tract. Symptoms of CD are abdominal pain with cramping, chronic diarrhea, lack of appetite/weight loss, fatigue, and fever [Baumgart and Sandborn, 2012; Podolsky, 2002]. Other symptoms may include mouth sores, rectal bleeding, perianal disease as well as inflammation of joints, skin, eyes, and liver/bile ducts. Crohn's disease is also

Correspondence to:

Bruce P. Burnett, PhD
Entera Health, Inc., 2000
Regency Parkway, Suite
255, Cary, NC 27518, USA
bruce.burnett@enterahealth.com
enterahealth.com

Ira Shafran, MD, PA
University of Central
Florida Medical School,
Orlando, FL, USA
Shafran Gastroenterology
Center, Winter Park,
FL, USA

Patricia Burgunder, ARNP
Shafran Gastroenterology
Center, Winter Park, FL,
USA

David Wei, PhD
WC, LLC, Cary, NC, USA

Hayley E. Young, PhD
Entera Health, Inc., Cary,
NC, USA

Gerald Klein, MD
Entera Health, Inc., Cary,
NC, USA

characterized by inflammation of joints, skin, eyes, and liver/bile ducts. Though UC is also characterized by inflammation of the GI tract it can be transmural in later stages with inflammation usually only in the epithelial layer of the colon. Symptoms of UC include progressive deterioration in consistency and urgency of bowel movements that can lead to persistent diarrhea, which is generally bloody with cramping, abdominal pain, tenesmus, and occasionally decrease appetite that may lead to weight loss [Crohn's and Colitis Foundation of America, 2015].

Currently, there is no cure for either type of IBD. Today's goal for the management of IBD is clinical remission defined as a long period of time without symptoms, avoiding flares of disease and improving the patient's quality of life [Crohn's and Colitis Foundation of America, 2015]. This type of remission is often assessed through patient reported outcomes. The ultimate goal in the care of IBD patients is complete or 'deep' remission, which includes clinical (symptom management), endoscopic (mucosal healing) and histological (microscopic evidence of tissue healing) management. Although there are attempts underway to standardize and develop validated scoring systems for endoscopic and histological remission, this remains an unrealized goal [Panaccione *et al.* 2013; Bryant *et al.* 2014].

As both UC and CD share the commonality of inflammation as well as other symptoms, many of the same therapies are used to treat both diseases. Typical treatments for CD and UC comprise a variety of therapeutics which target the body's immune response. These include anti-inflammatory agents, immunosuppressants, and immunomodulators [Engel and Neurath, 2010] as well as biologics that bind tumor necrosis factor (TNF)- α to damp immune activation or integrin $\alpha 4\beta 7$ to inhibit mucosal lymphocyte attachment [Moss *et al.* 2013; Soler *et al.* 2009]. Antibiotic therapy is sometimes utilized to treat IBD, especially for infections and fistulas (i.e. duodenocolic, enteroenteric, enterovesical, gastrocolic and rectovaginal as well as aortoenteric fistulas which occur after surgical graft placement).

Serum-derived bovine immunoglobulin/protein isolate (SBI) is the nutritional ingredient in a prescription medical food product intended to provide for distinctive nutritional requirements that are unique for the clinical dietary management of specific intestinal disorders [e.g. in irritable bowel syndrome with diarrhea (IBS-D), IBD and

HIV-associated enteropathy]. It must be administered under physician supervision [United States Food and Drug Administration]. The mode of action for this specially formulated bovine immunoglobulin preparation is multifaceted. SBI binds microbial components, maintains GI immune balance, manages gut barrier function and improves nutrient utilization [Petschow *et al.* 2014]. Clinically, SBI has been shown to reduce symptoms of abdominal discomfort, flatulence, bloating, loose stools and urgency in IBS-D [Wilson *et al.* 2013] as well as loose stools, cramping, urgency, incontinence and nocturnal bowel movements in HIV-associated enteropathy [Asmuth *et al.* 2013]. In addition, case studies of SBI report management in drug-refractory IBS-D patients in real-world settings [Hilal *et al.* 2014; Weinstock and Jasion, 2014; Good *et al.* 2015; Crawford and Panas, 2015]. Recent case series utilizing SBI in CD and UC patients to achieve clinical remission in patients who were not fully managed by traditional drug therapies [Awad and Jasion, 2015; Good and Panas, 2015] as well as potential endoscopic remission [Beauerle *et al.* 2015; Awad and Jasion, 2015]. Finally, animal models of colitis have confirmed the attenuating effect of SBI on inflammatory markers as well as on tissue structure [Pérez-Bosque *et al.* 2015; Henderson *et al.* 2015].

This case series reports the retrospective analysis of chart data accumulated from a relatively large CD and UC patient population in a single practice who were administered SBI to determine the overall effect on IBD symptom and disease management when added to their therapeutic regimens.

Methods

Patients

Patients diagnosed with IBD were from a single gastroenterology practice located near Orlando, FL. The initial chart review included 50 patients who were provided SBI at 5 g/day because they had not responded to traditional pharmaceutical intervention. These patients were being treated with a diverse number of traditional pharmaceutical therapies in combination including anti-TNF- α agents (i.e. adalimumab, infliximab, certolizumab pegol), anti-inflammatory medications (i.e. mesalamine and budesonide), as well as immunomodulators (i.e. azathioprine, 6-mercaptopurine), all of which did not fully manage their symptoms and were not achieving clinical remission [Crohn's and Colitis Foundation of America,

2015]. Patients experienced a variety of symptoms including abdominal pain, urgency, tenesmus, and fatigue. Persistent diarrhea was common to all patients in this analysis in addition to diminished quality of life due to their ongoing lack of symptom and disease management. Institutional review board review was not needed for this retrospective chart review since all patient identifying information was removed prior to processing the data, a practice permitted under 45CFR46.101(b)(4)(2009). All patients consented to use of their de-identified health information for the publication of this case series.

Nutritional standard-of-care

SBI is the nutritional ingredient in a prescription medical food (EnteraGam®) consisting of a specially formulated protein source (~92%) with >50% IgG, ~1% IgA, 5% IgM and other proteins typically found in milk. SBI is lactose, gluten, soy, casein, whey, and dye free. SBI is generally recognized as safe (GRAS), a requirement for medical food products [FDA, 2015], and has demonstrated safety in several clinical studies [Wilson *et al.* 2013; Asmuth *et al.* 2013; Lembcke *et al.* 1997; Begin *et al.* 2008; Earnest *et al.* 2005].

Statistics

Patients who are administered any new therapeutic in this practice were contacted at least monthly by phone and asked to assess their overall symptom management using a Likert scale (0 = none; 1 = minimal; 2 = moderate; 3 = significant; 4 = complete). At the same time, the patients were asked if they were taking their daily dose of SBI. Their responses represent patient-reported evaluation of their individual IBD symptoms. Patients were also asked to report side effects to SBI addition on a monthly basis. To retrospectively evaluate the statistical significance of reported symptom management of patients who were administered SBI, the assessments at week 1 were considered baseline and the last week for which patients reported data was termed the retrospective endpoint (week 12). Any patients who were administered SBI less than 12 weeks had their last observation carried forward. Baseline at week 1 is valid based on the known onset of action of 2–4 weeks reported for this product in clinical trials of IBS-D and HIV-associated enteropathy [Wilson *et al.* 2013; Asmuth *et al.* 2013]. In addition, anecdotal case reports suggest that a full

onset of action for IBD occurs between 4 and 8 weeks [Beauerle *et al.* 2015; Awad and Jasion, 2015; Good and Panas, 2015]. Analysis of variance (ANOVA) was used to compare patient response to SBI based on characteristics of gender (female *versus* male), race (Caucasian *versus* other) and age (≥ 65 years *versus* < 65 years). A multivariate ordered logistic regression model was then employed, with control for these characteristics, to calculate the odds ratio representing the likelihood of further symptom and disease management over and above the patient's response to current therapy.

Patient continuity and compliance

The average of numerical values associated with patient-collected responses for symptom management were plotted to retrospectively capture the overall trend of reported outcomes and to assess the effect of SBI on the entire cohort during the time period used in the statistical analysis. The percent change in the level of symptom management from week 1 to the 12 week endpoint was also plotted to compare the population response.

Results

The cohort analyzed ($N = 45$) in this chart review were provided SBI over 12 weeks and included patients with CD ($n = 38$) and UC ($n = 7$), ages 21–88 (mean = 51.5 years). There were 17 females and 41 identifying as Caucasian who reported responses at week 1 and at endpoint of analysis (week 12) (Table 1). About half of the CD patients were ileocolonic, ~40% were small bowel and a minority were large bowel in the population analyzed in this chart review. The UC patients had active disease with intermittent flares. The average duration of disease diagnosis in these patients was 17 years. SBI (5 g/day) was provided to patients in addition to their current therapy regimens for nutritional support of their disease. Patients were contacted at least monthly by phone and asked to assess symptoms in response to SBI using a Likert scale as part of normal practice. There were 5 patients who did not take the initial dose and provided neither baseline nor subsequent data when contacted. A majority of patients in this chart review remained on therapy well beyond the 12-week endpoint used for this analysis. There were no side effects reported in response to the 5 g/day dose of SBI. The demographic characteristics of

Table 1. Patient demographics and baseline characteristics.

Characteristic	Patients (N = 45)
Gender, n (%)	
Female	17 (37.8%)
Male	28 (62.2%)
Race, n (%)	
White	41 (91.1%)
Hispanic	2 (4.4%)
South Asian	2 (4.4%)
Age (years), mean (standard deviation)	51.5 (19.0)
Senior age group (≥ 65 years), n (%)	10 (22.2%)
Inflammatory bowel disease, n (%)	
Crohn's disease	38 (84.4%)
Ulcerative colitis	7 (15.6%)

Table 2. Management of inflammatory bowel disease in response to serum-derived bovine immunoglobulin/protein isolate.

Characteristics		Analyzed patients (n)	Baseline response, mean (SD)	p-value*	Response at 12 weeks, mean (SD)	p-value*
Gender:	Female	17	1.2 (1.1)	0.1949	1.4 (1.1)	0.7281
	Male	28	0.8 (1.0)		1.5 (1.2)	
Race:	Caucasian	41	1.0 (1.1)	0.1955	1.5 (1.1)	0.6659
	Other	4	0.3 (0.5)		1.3 (1.5)	
Age:	<65 years	35	0.9 (1.0)	0.7122	1.3 (1.1)	0.1089
	≥65 years	10	0.8 (1.1)		2.0 (1.2)	
*p-values were obtained from analysis of variance tests. SD, standard deviation.						

the 45 patients included in the retrospective analysis are shown in Table 1.

In addition to SBI, these patients were also utilizing diverse therapies in combination commonly used to treat IBD such as anti-inflammatory agents, immunomodulators, and biologics, but without sufficient management of their symptoms which reflected lack of clinical remission. The ANOVA comparison using the tiered scoring system for symptom management after the addition of SBI to patient therapeutic regimens is shown for baseline (week 1) and 12 weeks in Table 2 for each demographic. At baseline, patients' responses to SBI nutritional addition did not significantly differ by patient demographics (age, gender, race). At the end of the 12-week period, the average score of patients' responses improved across all patient demographics, but differences in response to SBI

between subcategories of age, gender and race remained similar.

To test the statistical significance of overall management from baseline to the 12-week endpoint for analysis, a multivariate ordered logistic regression model was employed with control for patient characteristics, including patient age (≥ 65 years *versus* < 65 years), gender (female *versus* male), race (non-Caucasian *versus* Caucasian), and diagnosis (CD *versus* UC). This model was chosen as the patient reported data was based on correlation to further overall disease management with the addition of SBI and did not depend on prior or concomitant therapies. Based on the calculated odds ratio, all patients in this retrospective chart review were 2.8 times more likely to report clinical improvement in symptom scores in response to SBI at 12 weeks even while on other therapeutics [95% confidence interval (CI) 1.266–6.016,

Table 3. Odds ratio estimates in ordered logistic regression.

Parameter	Odds ratio (95% confidence interval)
Retrospective endpoint (week 12) <i>versus</i> baseline (week 1)	2.8 (1.266–6.016)*
Female <i>versus</i> male	1.2 (0.547–2.774)
Non-Caucasian <i>versus</i> Caucasian	0.3 (0.057–1.487)
Age ≥ 65 <i>versus</i> age < 65	1.1 (0.421–2.924)
Diagnosis of Crohn's disease <i>versus</i> ulcerative colitis	0.3 (0.108–1.108)

* $p = 0.011$.

Figure 1. Average reported improved response of all inflammatory bowel disease patients ($N = 45$).

$p = 0.011$] (Table 3). This finding was significant compared with the null hypothesis corresponding to an odds ratio of 1 in which patients would have equal likelihood of reporting the same or worse disease management at 12 weeks as they did at baseline. This model also showed that response to SBI addition was not associated with age, gender, race or diagnosis.

To retrospectively capture the overall pattern of reported clinical management for the entire cohort during the time period used in the statistical analysis, average patient-reported symptom management with addition of SBI was determined according to time. The average group response to therapy was calculated using symptom management scores and plotted over time (Figure 1). This pattern of improvement over and above the insufficient treatment outcomes prior to the addition of SBI demonstrates that there is continued reduction in clinical symptoms up to 10 weeks at 5 g/day. When the percent symptom improvement was plotted, there was a dramatic shift in responders found at week 1 (49%) *versus* the week 12 endpoint (76%). In addition, the percentage of patients experiencing significant management improved from 9% to 20% over the 12 week retrospective analysis (Figure 2).

Figure 2. Per cent change in disease management at week 1 *versus* week 12.

The overall response to the addition of SBI in IBD patients suggests that the longer patients are on therapy, the better their outcomes. It is possible that addition of SBI with other therapies used concomitantly resulted in further or even synergistic benefit in these patients. Further clinical research is needed to assess SBI's effects in combination with other treatments for IBD.

Discussion

The pathogenesis of IBD is not completely understood. There is, however, a growing body of evidence suggesting that IBD arises from complex interaction between host genetic susceptibility and alterations in the gut microbiome or diet, which leads to a chronic state of inflammation associated with barrier dysfunction [Lepage *et al.* 2011; Moussata *et al.* 2011; Leone *et al.* 2014; Devkota *et al.* 2012; Zeissig *et al.* 2007]. Even with the advent of effective treatments for IBD, there is still a need for new, safe therapeutics to manage patient conditions.

Evidence for the use of SBI in IBD is based on animal and human studies. An oral

immunoglobulin-containing plasma formulation, a 50% pure IgG formulation (IC) similar to SBI, and a control diet were all tested in a *mdr1*^{-/-} knockout (KO) mouse model of spontaneous colitis and compared with outcomes in wild-type (WT) mice [Perez-Bosque *et al.* 2015]. When the immunoglobulin-containing plasma or IC formulations were given orally, there was a significant reduction in the expression of cytokines interleukin (IL)-2 and IL-17, chemokines MCP-1 and MIP-1b, and iNOS in the mucosa. There was also a reduced percentage of activated Th lymphocytes in the lamina propria as well as interferon (IFN)- γ and TNF- α expression in the colon. In another animal model, altered Schaedler flora mice were fed SBI or hydrolyzed collagen as a control followed by an *Escherichia coli* LF82 provocateur originally isolated from a CD patient and then dextran sodium sulphate (DSS) to induce colitis [Henderson *et al.* 2015]. SBI consumption resulted in significant modulation of colonic inflammation ($p < 0.01$), colon mucosal height ($p < 0.05$), cecal stromal collapse ($p < 0.05$), and colonic glandular hyperplasia ($p < 0.05$) in DSS treated mice compared with those fed hydrolyzed collagen at the same level. Serum markers for acute gut inflammation and epithelium damage, serum amyloid A protein ($p = 0.0006$), intestinal fatty acid binding protein ($p = 0.0003$) and IL-6 ($p < 0.05$), were statistically lower levels in DSS-induced mice fed SBI as compared to hydrolyzed collagen. Local cecal granulocyte-colony stimulating factor (G-CSF) levels also trended lower in animals fed SBI *versus* hydrolyzed collagen. These results support a local as well as a systemic effect in modulating inflammatory factors in colitis animal model.

In support of the results from animal studies, recent case histories report SBI-mediated disease management in UC and CD patients [Beauerle *et al.* 2015; Awad and Jasion, 2015; Good and Panas, 2015]. One UC patient experiencing 10–15 watery stools per day with frequent bleeding incorporated SBI into her therapy regimen and had a dramatic management response: 1–2 formed bowel movements per day, and cessation of further bleeding or abdominal cramps [Beauerle *et al.* 2015]. Furthermore, there was strong reduction in erythrocyte sedimentation rate as well as visual evidence of mucosal healing (Mayo Grade 2 ulcerative colitis pre-SBI to grade 0 post-SBI). Another UC patient who had 5–10 bloody stools per day with tenesmus and

cramping was only controlled on high-dose oral steroids in combination with adalimumab [Awad and Jasion, 2015]. When steroids were removed, the patient had flares of bloody stools and other symptoms. When placed on 5 g twice daily of SBI in combination with adalimumab and steroids, the patient's symptoms subsided, steroids were completely tapered and the patient exhibited normal mucosa upon repeat colonoscopy compared with highly inflamed tissue prior to SBI addition to therapy. There are additional reports of SBI use in CD and UC patients who were incompletely managed on traditional therapies for chronic loose and frequent stools [Good and Panas, 2015] similar to the population studied here. These patients reported better overall disease management specifically in terms of stool frequency, ileostomy output, and appropriate weight gain with the addition of SBI. With this as supportive information for the use of SBI in IBD, the protein formulation was used as nutritional support for patients in this clinical practice. The findings here are significant due to larger patient population compared with previous case studies but also illustrate the use of SBI in patients with incomplete clinical response to traditional drug therapies.

Patient-reported outcomes are still the standard for clinical remission in IBD [Panaccione *et al.* 2013]. Therefore, this analysis using a Likert scale in this gastroenterology practice to judge response of any new therapeutic added to patients' treatment regimens fits the current paradigm of assessing the effect of any agent on IBD symptom management. The patient reported outcomes collected in this retrospective evaluation were statistically analyzed using multivariate ordered logistic regression model to better determine patient response to therapy. This method of interpreting the data assessed the likelihood that a patient's response to therapy for overall clinical improvement in symptoms scores and hence, disease management, would be increased from baseline by the retrospective endpoint and does not depend on other therapies the patient is on concomitantly or prior to SBI administration. Conversely, it does not reflect patients who may have consistently reported a significant improvement in symptoms for the duration of analysis. This type of analysis also tends to eliminate any bias generated by patients who may have had a strong initial response due to a placebo effect.

All patients receiving SBI were followed in the same manner and asked to report on the same symptom management scale. In addition, SBI was administered as an add-on therapy in patients who continued to have incomplete resolution of symptoms even while on combinations of various other agents including anti-inflammatory medications, immunomodulators and biologic therapies. As this was a retrospective analysis and no control group was available, the patient responses to SBI at 1 week were compared with those collected up to the retrospective endpoint of 12 weeks. Using week 1 as the baseline time point was projected from the onset of action from studies in IBS-D and HIV-associated enteropathy patients, divergent patient types with different forms of disease [Wilson *et al.* 2013; Asmuth *et al.* 2013]. This commencement of symptom reduction was also observed in case study observations in CD and UC patients [Beauerle *et al.* 2015; Awad and Jasion, 2015; Good and Panas, 2015] who reported similar symptom control including chronic loose and frequent stools after 2–4 weeks but using higher doses of SBI (5 g QID or 5 g BID), which may increase onset of action and provide further management over and above 5 g/day. In this retrospective analysis of data at baseline and at endpoint, patients were nearly three times (2.8) more likely to report further statistical disease management after 12 weeks of SBI therapy compared with baseline (week 1) ($p = 0.011$), bearing out the results found from clinical findings for SBI in other diseases. Although the incidence of IBD is higher in Caucasians than non-Hispanic Blacks, Hispanics, or Asians [Wang *et al.* 2013], Ghazi and colleagues have previously shown that African Americans have a similar disease activity, quality of life score, and do not represent a more severe group of patients than Caucasians [Ghazi *et al.* 2014]. There is not expected to be a different response in Hispanic or South Asian populations studied here. Indeed, in this analysis there were no effects of administration after 12 weeks based on race ($p = 0.1629$), age ($p = 0.1089$), or gender ($p = 0.8221$).

Overall management with SBI in this study, as well as in the other reports of its use in IBD models [Perez-Bosque *et al.* 2015; Henderson *et al.* 2015] and clinical cases of IBD [Beauerle *et al.* 2015; Awad and Jasion, 2015; Good and Panas, 2015], is likely due to the unique dietary protein composition which provides distinctive nutrients required for disease management in these patients. The mechanism of action of SBI is thought to

involve binding microbial components, maintaining GI immune balance and managing gut barrier function [Petschow *et al.* 2014]. By managing gut barrier function, SBI utilization ultimately results in greater nutrient uptake [Asmuth *et al.* 2013; Lembcke *et al.* 1997; Begin *et al.* 2008], utilization and better fluid balance as evidenced by a reduction in chronic frequent and loose stools [Wilson *et al.* 2013; Asmuth *et al.* 2013; Beauerle *et al.* 2015; Awad and Jasion, 2015; Good and Panas, 2015]. While the depth and anatomic location of the disease may vary between CD and UC, the commonality of inflammation and symptomology links these diseases. Though a larger study with multiple centers and a control group is desired, cases series such as this one may be a ‘real-world’ reflection of therapeutic response in everyday practice in patients with comorbidities and who are on polypharmacy. Limitations of this chart review include the lack of a validated instrument to judge clinical remission, no endoscopic analysis of patients before as well as after administration of SBI, lack of a good way to enforce adherence and no placebo control as this was an open-label observation of patients in a community setting. Another limitation of this analysis is that the patient population may not represent a larger real-world IBD population. The results from this retrospective analysis, as well as other anecdotal reports [Beauerle *et al.* 2015; Awad and Jasion, 2015; Good and Panas, 2015], however, suggest the use of SBI provides for a distinctive nutritional requirement unique to these populations for the management of IBD. Meanwhile, due to an important limitation of small sample size in this study, caution must be taken when interpreting the results above. A larger study with a control group is recommended in a future investigation.

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Conflict of interest statement

Dr Shafran is a speaker for Entera Health, Inc. Drs Young, Klein, and Burnett are employees of Entera Health, which markets SBI. Dr Wei is a pharmacoeconomist who provided statistical assistance. Shafran and Burgunder were responsible for data

collection. Data analysis was performed by Wei, Young, Klein and Burnett. Each author contributed equally to the interpretation of the data, writing, editing and approval of this manuscript.

Informed consent

All patients whose charts were used in this retrospective case series were informed with regard to the submission of this manuscript and shown a copy.

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