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Long-term Management of Pouchitis-Associated Diarrhea with Serum-Derived Bovine Immunoglobulin/Protein Isolate

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Abstract

For many patients with inflammatory bowel disease, the need for a proctocolectomy with the establishment of a J-pouch is a necessary procedure. In some patients, an inflammatory condition of the J-pouch known as pouchitis contributes to symptoms that include bloody diarrhea, urgency, dehydration and endoscopic evidence of inflammation. The specific cause of pouchitis is unknown, and there is also no universally accepted or FDA-approved treatment for pouchitis. As such, many patients are managed empirically with multiple medication regimens. Ten patients with pouchitis, who experienced flares and poor management of their condition with conventional drug treatments, had severe, unremitting chronic diarrhea. It was not until the addition of serum-derived bovine immunoglobulin/protein isolate (SBI) that 8 of 10 patients experienced satisfactory management of their pouchitis-associated diarrhea. An ongoing analysis of 7 of these 10 patients for up to 5 years found that 5 of these patients experienced ongoing management of their diarrhea associated with pouchitis with no reports of any flares with the remaining 2 patients reporting a few minor flares. One patient out of the 5 analyzed was able to discontinue all adjunctive therapies. Three of the 10 original patients were lost-to-follow up or moved out of state and no further details were available for ongoing analysis. As a medical food, SBI is not intended for the specific treatment of pouchitis, but these patients demonstrate beneficial effects in the long-term management of diarrhea-associated with pouchitis.

Keywords: Pouchitis; Immunoglobulin; Remission; Diarrhea; Refractory

Introduction

Pouchitis is a medical condition associated with an inflammation of the intestinal mucosa of the ileal reservoir [1]. For refractory patients with ulcerative colitis, a total proctocolectomy with an ileoanal anastomosis (J-pouch) is a common surgical procedure [2-6]. While there is high patient satisfaction after this procedure, 30-60% of these patients experience pouchitis [4-6]. While the specific cause of pouchitis is unknown, common symptoms include the presence of bloody diarrhea, urgency, dehydration as well as endoscopic evidence of erythema of the mucosal pouch [4-6]. Despite the lack of a definitive cause, pouchitis may result from toxin release after bacterial dysbiosis, degradation of products, changes in intraluminal pH, low immunoglobulin levels, or other yet undetermined factors [4-8]. This lack of a clear etiology of pouchitis, may help explain why there is no formal FDA-approved treatment.

Lacking approved therapies, physicians are left to address patient symptoms based upon personal experience and suggestions from other opinion leaders in the management of pouchitis as well as limited

clinical data. Antibiotics such as ciprofloxacin and metronidazole are often used as first line therapy [8]. Additional options include systemic and topical steroids, budesonide, topical mesalamine, and VSL#3 [9]. Serum-derived bovine immunoglobin/protein isolate (SBI) is not commonly considered for the management of pouchitis and its associated diarrhea, but SBI has been seen to provide beneficial effects when used in patients with pouchitis or IBD-related conditions where diarrhea is the primary symptom [10-16].

The use of medical foods has been shown to have a distinct role in the management of gastrointestinal conditions [17]. SBI is produced and purified from pooled USDA-approved, edible-grade bovine plasma containing ~60% immunoglobulins (>50% IgG, 1% IgA and 5% IgM) along with other proteins and peptides that are similar to those commonly consumed by humans in beef products [18]. EnteraGam®, a medical food product intended for the dietary management of chronic diarrhea and loose stools, contains 5 g of SBI and 5 g of dextrose with trace amounts of sunflower lecithin per packet [18]. SBI's primary mode of action is the binding of microbial components (i.e., bacterial toxins). This has a downstream effect of reducing inflammatory markers and the restoration of tight junctions between epithelial cells [19]. As a result (Figure 1), SBI has been shown to help maintain and support barrier function within the gastrointestinal tract in patients with chronic loose and frequent stools [20-22].

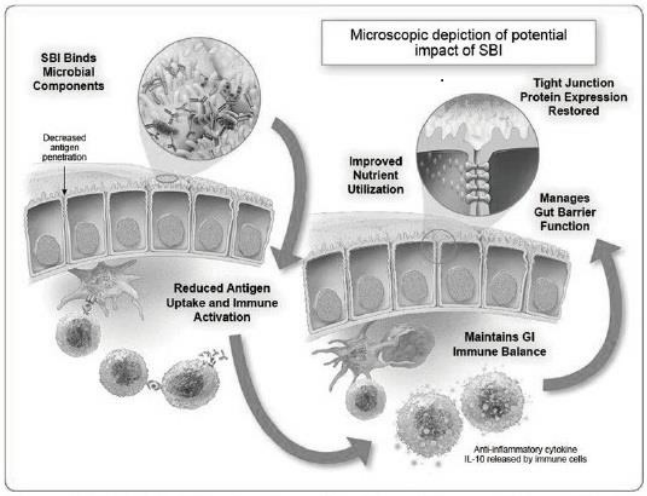

Figure 1: Postulated mechanism of action including microbial binding and cascade effect to tight function restoration, [Used with permission from RedHill Biopharma].

Aims

Based upon the growing experience of physicians using medical foods, SBI appears to have potential application for the management of chronic diarrhea associated with pouchitis.

This was considered in this retrospective review of 10 patients, who have utilized prescribed EnteraGam® (SBI) as part of the management plan for pouchitis-associated diarrhea and the eventual long-term management for the remission of their condition.

Methods

Pouchitis patients who had failed to adequately respond to conventional therapy (antidiarrheal agents, antibiotics, budesonide) were considered for the addition of SBI as part of their standard of care in order to try to manage their pouchitis-associated diarrhea and potentially establish remission. All patients were initially followed for one year and continued to be followed for several additional years as part of the standard of care with SBI.

The retrospective chart review of these 10 patients was based upon an initial assessment of SBI in patients with pouchitis. Given the initial response in these patients, the ongoing review was to determine if they continued to respond over the long-term use of SBI for their pouchitis associated symptoms.

Results

These 10 patients initially lacked a response to conventional therapies for their diarrhea-associated pouchitis symptoms. The individual outline of the history of the patients' pouchitis and efforts to manage the condition included ciprofloxacin, budesonide and/or other typical measures but failed to achieve remission (Table 1). For many of these patients, drug treatments including antidiarrheal agents, antibiotics and budesonide helped to manage their pouchitis condition, but they continued to experience pouchitis flares that resulted in severe diarrhea.

Several patients had experienced symptomatic pouchitis flares for many years without satisfactory response to conventional therapies. It was not until the addition of SBI (5 g QD or BID) that 8 of 10 patients achieved clinical, asymptomatic remission of their pouchitis as judged by management of chronic diarrhea and lack of other symptoms along with endoscopic remission documented in 2 of these patients during the first year of therapy (Table 2).

Table 1: Patient and disease history prior to SBI therapy; [UC: Ulcerative colitis].

No.	Patient	Disease History
1	57-year-old Caucasian Male	UC History since 2001. Pouchitis occurring 2-3 times/year with urgency, blood and mucus. Treated with ciprofloxacin and/or budesonide without satisfactory relief.
2	67-year-old African American Female	UC history since 2006. Proctocolectomy and J-pouch with ileoanal anastomosis. Chronic pouchitis with cramps, urgency, frequent small stools/day, mucus and blood. Treated with pulse antibiotics, ciprofloxacin, and nitazoxanide. Maintenance therapy with budesonide with marginal success. Pouchoscopy-superficial ulceration, mucosal erythema, friability, Biopsy-active ileitis with nodular hyperplasia and reparative glandular changes.
3	47-year-old Caucasian Male	History of severe refractory UC since 1999. Total proctocolectomy and J-pouch with ileoanal anastomosis. Frequent pouchitis episodes with urgency, mucus and bloody stools. Treatment included ciprofloxacin, nitazoxanide, and budesonide. Pouchoscopy with biopsy-pouchitis and cryptitis with increased lymphoid aggregates.
4	62-year-old Caucasian Female	History of Lynch Syndrome with multiple malignant colon polyps. Total proctocolectomy and J-pouch with ileoanal anastomosis in 2005. Frequent episodes of pouchitis with urgency, bloody stools with mucus, and fecal incontinence. Treated with ciprofloxacin and budesonide.
5	69-year-old Caucasian Male	History of severe UC refractory to therapy. Total proctocolectomy and J-pouch with ileoanal anastomosis in 2002. Frequent exacerbation of pouchitis with bleeding, urgency, and fecal incontinence. Treatment included ciprofloxacin and budesonide. Despite treatment-recurrent pouchitis flares 3-4 times/year.
6	60-year-old Caucasian Male	History of severe refractory UC with total proctocolectomy and J-pouch with ileoanal anastomosis in 2012. Frequent pouchitis episodes and food-triggered diarrhea. Treated with alosetron, diphenoxylate-atropine, paregoric, cholestyramine and ciprofloxacin.
7	24-year-old Caucasian Male	March 2014 – diarrhea noted with rectal bleeding for 6 weeks. Flexible sigmoidoscopy revealed Mayo Grade 3 ulcerative pouchitis with confirmatory histology on biopsy.
8	59-year-old Caucasian Male	Total proctocolectomy and ileoanal anastomosis but post-op difficulty to control diarrhea with occasional fecal incontinence and dietary intolerance to large meals, fatty foods, and dairy products. Several pouchitis episodes treated with paregoric, diphenoxylate-atropine, and/or loperamide. December 2014-severe diarrhea with 7-8 loose bowel movements/day on treatment regimen including the addition of alosetron.
9	48-year-old Caucasian Male	History of UC. Total proctocolectomy with ileoanal anastomosis with frequent pouchitis for 8 years. Treated with antibiotics and budesonide. Asymptomatic approximately 3 months between pouchitis episodes.
10	69-year-old African American Female	History of UC. Total proctocolectomy with ileoanal anastomosis in 2008. Chronic, unremitting pouchitis episodes since surgery. Pouchoscopies and biopsies-gross and histologic chronic inflammatory changes. Treated with budesonide with poor response and pulse antibiotic therapy worsened symptoms.

One patient was generally asymptomatic during the first year but had one flare that was resolved with a 10-day course of antibiotics in addition to the SBI. A second patient had significant improvement in the clinical symptoms of pouchitis noting 11 months of remission but was eventually lost-to-follow-up.

All patients continued with SBI therapy with 8 of them using SBI as monotherapy to manage their pouchitis condition. During the second year of treatment, 8 of the 10 patients continued without any flares and 2 more patients were lost-to-follow-up. Of these 2 patients, one had been symptom-free for 11 months at the last report and the second patient had been symptom-free for over a year (Table 2). Over the long-term, 7 of the original 10 patients were monitored. For the other three, two were noted as lost-to-follow-up during the second year of therapy and one patient eventually moved out of state after being symptom-free and followed for more than 2 years.

Of these remaining 7 patients, 5 patients continued to be well managed on SBI therapy for pouchitis-associated diarrhea with three patients reporting no flares for over

4 years. One patient was treated for over 5 years and had no significant reports of flares over the long-term. One patient was treated for over 3 years without any reports of flares. The 2 remaining patients both reported at least 2 flares during the long-term period. One patient had been treated for over three years during which time two flares were reported. Budesonide was added to the SBI therapy for 14 days and both times the flares resolved.

In the second patient treated for over 4 years, there were reported a few flares generally lasting 2-3 days. Ciprofloxacin was added to the therapy during which the flares resolved. Overall during this long-term review of patients, pouchitis symptom improvements were noted within 2 to 3 weeks of therapy initiation for 8 of 10 patients. As such, maintenance therapy of SBI (5 g QD or BID) for chronic diarrhea has allowed 8 of 10 patients to continue remission for more than 2 years. Three patients were lost-to-follow over time.

Of the remaining 7 patients, there were no issues in 5 of 7 patients and 2 of 7 required an occasionally adjunctive drug therapy to help manage a few minor flares. Flares were generally mild and limited. Of these 7 patients, one was treated for over 5 years without a flare.

Three patients were treated for over 4 years with only one having an occasional mild flare which required the addition of a short-term antibiotic treatment. Two patients were treated for over 3 years with one patient reporting 2 flares during the time period. Six of 7 patients continued SBI therapy and one patient discontinued all therapy for their pouchitis and continues to be symptom free.

Table 2: Patient disease management with SBI therapy; [BID: Twice a day; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; g: Grams; prn: As needed; QD: Once a day; Q7-14D: Once every 7-14 days; SBI: Serum-derived Bovine Immunoglobulin/Protein Isolate; UC: Ulcerative Colitis].

No.	Patient	Disease History with SBI Therapy	Remission Status		
			Year 1	Year 2	Long-term
1	57-year-old Caucasian Male	Oct. 2013 - treated with ciprofloxacin 500 mg BID x 10 days and SBI 5 g/day. Symptoms resolved and SBI continued. June 2014-Pouchitis flare occurred: pouchoscopy revealed severe mucosal inflammatory changes. Biopsy noted severe acute and chronic inflammation with cryptitis and crypt distortion. Treated with ciprofloxacin x 10 days along with SBI 5 g BID allowing for remission of symptoms. Over the 4-year period with SBI (July 2014-SBI 5 g BID monotherapy) has been stable but developed Parkinson Disease. Episodes of self-limited abdominal distension treated with Trulance 3 mg Q/7-14D.	1 flare after 9 months. Remission reestablished within 2 weeks with 10-day antibiotic therapy.	No flares	No recurrent episodes of pouchitis reported over 4-year period.
2	67-year-old African American Female	Due to persistent recurrence of symptoms, SBI 5 g BID was added allowing for clinical remission. Budesonide was discontinued after 2 months and no antibiotic therapy has been necessary. Currently using SBI 5 g BID and Bentyl (prn) for abdominal pain. Developed a cardiovascular morbidity leading to an AICD placement. A multi-modular goiter	No flares	No flares	No evidence of recurrent pouchitis over the 4-year period.

		has developed and is under evaluation. Routine pouchoscopy scheduled.			
3	47-year-old Caucasian Male	SBI 5 g BID initiation allowed for remission of symptoms. No antibiotic or corticosteroid therapy has since been needed. SBI 5 g BID monotherapy continued and was eventually transitioned to SBI 5 g QD. The patient works full time and the recent pouchoscopy revealed no significant pouchitis and a biopsy reveal normal small bowel mucosa with mild chronic inflammation.	No flares	No flares	No significant pouchitis reported in 5-year period. No need for steroid or antibiotic therapy.
4	62-year-old Caucasian Female	Due to a flare in May 2014, SBI 5 g BID was added and complete resolution of symptoms was noted within 6 weeks. No recurrence noted and no additional therapies required. SBI 5 g BID monotherapy continued. In January 2017 given no episodes of pouchitis, SBI was discontinued.	No flares	No flares	No episodes of pouchitis in 4 years. All therapies discontinued.
5	69-year-old Caucasian Male	Oct. 2013, treated with ciprofloxacin x 10 days along with SBI 5 g BID. Clinical remission of pouchitis noted with no exacerbation or recurrence. SBI 5 g BID monotherapy continues.	No flares	No flares	No episodes of pouchitis in 3 years.
6	60-year-old Caucasian Male	Nov. 2013 - SBI 5 g BID added to therapy approximately 1-year post surgery. Clinical remission of symptoms reported and fewer food-triggered episodes of diarrhea. No antibiotic therapy necessary. Subsequently, the patient has developed Parkinson's Disease. Pouchitis therapy continues as 5 g BID since 2013.	No flares	No flares	In 3 years, there had been two episodes of pouchitis flares. Both were treated with the addition of budesonide for 14 days.
7	24-year-old Caucasian Male	Treated with mesalamine x 14 days along with SBI 5 g QD allowing for remission of symptoms. Follow-up flexible sigmoidoscopy and biopsy demonstrated endoscopic and histologic remission (Mayo grade 0). Labs including ESR and CRP were all normal. SBI 5 g QD monotherapy continues	No flares	No flares	Moved out of state
8	59-year-old Caucasian Male	Dec. 2014 - within three weeks after adding SBI 5 g/day, bowel movements improved with 2-3 soft bowel movements daily. April 2015 - pouchoscopy and biopsy revealed mild distal mucosal erythema with mild-moderate histologic evidence of inflammation.	Clinical improvement on SBI therapy over 11 months but clinical remission not fully established.	Lost to Follow-up	Lost to Follow-up

9	48-year-old Caucasian Male	Aug. 2013 endoscopy noted pouchitis and SBI 5 g BID initiated resulting in clinical remission. Prior to SBI therapy, remission had not occurred for more than 3 months at a time. Patient has been maintained on SBI 5 g BID with an occasional short-term dosage of ciprofloxacin for mild flares. Recent pouchoscopy revealed no evidence of pouchitis.	No flares	No flares	In 4 years there had been some mild flares of pouchitis lasting 2-3 days. Flares treated with antibiotic therapy.
10	69-year-old African American Female	Jan 2015, SBI 5 g BID was initiated resulting in asymptomatic condition with 2-3 formed stools Feb 2015 - budesonide discontinued and no antibiotic therapy needed. SBI 5 g BID monotherapy continues.	No flares	Lost to Follow-up	Lost to Follow-up

Discussion

Pouchitis is a challenging condition for patients who have gone through the surgical procedure establishing the J-pouch. Nearly 30-60% will experience symptomatic flares within the first year. Without an approved therapy, physicians have utilized a variety of therapeutic agents to help manage the symptoms associated with pouchitis.

These conventional therapies do not provide a satisfactory response and many patients experience repeated flares in their symptoms. For these 10 patients evaluated for over 3 years and one patient for as long as 5 years, the addition of SBI provided the necessary support to manage chronic diarrhea associated with pouchitis when conventional therapy failed to achieve remission.

It was not until the addition of SBI that 10 of 10 patients reported clinical improvement within the first year of therapy with 8 of 10 achieving clinical, asymptomatic remission. Nearly all (8 of 10) patients-maintained remission on SBI during the second year with two patients being lost to follow-up. One patient moved out of state after 2 years on therapy without any reported flares.

Of the remaining patients, 5 of 7 continued to be asymptomatic for as long as 3-5 years and 2 of 7 patients had some limited pouchitis flares that were resolved with adjunctive drug therapy. SBI monotherapy was the standard course of care in 4 of 7 patients with one patient being removed from all therapies and two patients requiring minimal adjunctive drug therapy during a flare.

Conclusion

Unlike common dietary proteins, microbial binding capacity provided by SBI is thought to lead to a cascade of effects: minimizing immune activation, reducing proinflammatory cytokines, and restoring tight junction barrier function. This mechanism of SBI though these actions may provide the necessary effect that potentially removes the trigger for the inflammatory flares in pouchitis patients resulting in diarrheal symptoms thus allowing many patients to achieve not only clinical remission but also endoscopic and histological remission.

The use of medical foods continues to find application within the management of gastrointestinal disorders. SBI may be a valuable option to support the long-term management of chronic diarrhea in pouchitis patients, especially given the lack of any formal approved therapy for pouchitis itself. While pouchitis itself is not currently part of the labeling for SBI (EnteraGam®), it is labelled for dietary management of chronic diarrhea and loose stools that is often associated with pouchitis and pouchitis flares.

As such, the use of SBI in this patient population may be warranted to manage diarrhea associated with pouchitis and pouchitis flares. This assessment in 10 pouchitis patients supports the important role of SBI in the initial and long-term diarrheal management of patients with pouchitis.

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Author's Contribution

Dr. Good contributed to the collection of the data and presentation of the information. Dr. Panas contributed to the summarization of the content and presentation of the data. Both authors contributed to the review and overall content within the manuscript.

Conflict of Interest

None declared.

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