Seminars in Colon and Rectal Surgery 28 (2017) 138–141

Contents lists available at ScienceDirect

Seminars in Colon and Rectal Surgery

journal homepage: www.elsevier.com/locate/yscrs

Treatment of chronic and refractory pouchitis

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A B S T R A C T

Chronic and refractory pouchitis are the most challenging phenotypes of pouch inflammation, which represent the worst end of the disease spectrum of pouchitis. There are multiple factors are associated with the development and disease course of chronic and refractory pouchitis. Those factors include the use non-steroidal anti-inflammatory drugs, *Clostridium difficile* infection, cytomegalovirus infection, presence of concurrent immune-mediated disorders, and pouch ischemia. The identification of those factors helps direct proper therapy.

Introduction

Pouchitis is the most common complication in patients with ulcerative colitis (UC) who have colectomy with ileal pouch-anal pouchitis (IPAA).[1–4] It is reported an annual incidence of up to 40%.[5] Oral broad-spectrum antibiotic therapy has been the mainstay for the treatment of patients with acute pouchitis. However, we encountered a growing number of patients with pouchitis who lost response to antibiotic therapy and developed refractory disease or chronic antibiotic-refractory pouchitis (CARP). The treatment of CARP has been challenging and various agents have been used, including dual antibiotic therapy with a prolonged course, mesalamines, corticosteroids, immunomodulators, and biologics. CARP is one of the most common causes of pouch failure.[6]

When patients with pouchitis fail to respond to antibiotic therapy, there are several strategies to address the issue. Fecal bacterial culture and sensitive test has been advocated to identify suitable antibiotics.[7] It is important to evaluated secondary factors associated with an antibiotic-refractory course, such as NSAID use,[8,9] concurrent pouch surgery-related mechanical complications (such as ischemia,[10] stricture, fistula, and anastomotic sinus), infection of *Clostridium difficile* or cytomegalovirus and the presence of other immune-mediated disorders [e.g., primary sclerosing cholangitis (PSC) and celiac disease].[9,11–13] Chronic pouchitis may be associated with concurrent mechanical or structural disorders of the pouch, such as strictures and anastomotic sinus. For example, pouch outlet obstruction (such as anastomotic stricture), can be associated with pouchitis, presumably due to bacteria overload from prolonged fecal stasis. The release of the obstruction, often along with concurrent antibiotic therapy, may promote the resolution of pouchitis.

Antibiotics

Antibiotics and probiotics are used for the induction and maintenance therapy for acute or acute relapsing pouchitis.[5,14–17] Relapse of pouchitis or recurrent pouchitis is common, after the treatment or resolution of the initial therapy.[18] An estimated 5–19% of patients with acute pouchitis develop treatment refractory or a frequently relapsing phenotype of pouchitis.[19–21]

The most commonly used antibiotic agents include ciprofloxacin, metronidazole, tinidazole, and rifaximin. CARP, by definition, is refractory to therapy with 2-week, single antibiotic therapy.[22–28]

The treatment of CARP has been challenging. CARP has been treated with various combined antibiotic regiments with a prolonged course. An open-label combination therapy using ciprofloxacin and metronidazole for 4 weeks was effective in treating pouchitis and backwash ileitis in patients with or without PSC.[29] Twelve patients (86%) experienced symptomatic remission and there was a reduction in the length of pre-pouch ileitis with 9 patients (64%) patients.[29] A 4-week therapy with combined ciprofloxacin (1 g/d) and metronidazole (1 g/d) has also been reported in the treatment of CARP with success.[30] A 4-week trial of ciprofloxacin and tinidazole (1–1.5 g/d) in 16 consecutive patients with CARP showed a greater reduction in the PDAI scores and greater improvement in quality-of-life scores than the controls treated with topical mesalamine. The rate of clinical remission and clinical response for the antibiotic group was 88% and 88%,

The author has received honoraria from Abbvie, Janssen, Salix, and research grant from Takeda.

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http://dx.doi.org/10.1053/j.scrs.2017.05.006
1043-1489/

respectively. However, 2 patients in the antibiotic group developed peripheral neuropathy and dysgeusia.[34] In addition, the treatment of CARP with a 4-week course of ciprofloxacin (1 g/d) combined with rifaximin (2 g/d) was also reported by 2 separate groups of investigators,[31,32] A 4-week treatment with a combination of ciprofloxacin (1 g/d) of rifaximin (2 g/d) was described in 2 studies.[31,32]

We can safely state that a combined antibiotic therapy with a prolonged course is more effective in treating CARP than the routine 2-week course with single antibiotic agent. However, data on their long-term efficacy, that is, beyond 4 weeks, are not available. There have been concerns about the efficacy and safety of long-term antibiotic use.

Mesalaimines

Few published studies on the treatment of CARP with 5-aminosalicylates. In an open-labeled study of oral sulfasalazine 3 g/d in 11 eligible patients with acute pouchitis with the pouchitis disease activity index (PDAI) score >7, 7 (63%) achieved remission at 8 weeks. At 8 weeks, the PDAI score was reduced from 11.2 $\pm$ 2.3 to 6.6 $\pm$4.7.[33] Topical mesalamine enema has been used as a control arm in randomized clinical study of oral ciprofloxacin and tinidazole for CARP. In the 10 mesalamine group, patients were treated with oral (4 g/d), enema (8 g/d), or suppository (1 g/d). In the mesalamine group, there was a significant reduction in the total PDAI scores. The rate of clinical remission and clinical response in the mesalamine group were 50% and 50%, respectively.[34] Due to their favorable safety profile, oral or topical mesalamines may be tried in patients with CARP.

Corticosteroids

CARP has been treated with topically active corticosteroids. In a study from Italy, 20 patients with CARP were treated with controlled ileal-release budesonide 9 mg/d for 8 weeks showed a significant reduction of median total PDAI scores after therapy, from 14 (range: 9–16) to 3 (range: 2–10) and an improvement in the median inflammatory bowel disease questionnaire (IBDQ) score, from 105 (range: 77–175) to 180 (range: 85–220).[35] Diffuse pouchitis with enteritis can be associated with backwash ileitis, particularly in patients with concurrent PSC, which is often refractory to antibiotic therapy. Our group conducted an open-labeled study of ileal-release budesonide (9 mg/d $\times$ 1–3 month for induction and 3–6 mg/d for 9 month) in 18 pouch patients with UC and PSC. While there were no significant change in liver enzymes and the revised Mayo Risk Score for PSC at 1 year, there was a significant improvement in the endoscopy subscores in the afferent limb and pouch body.[36]

Despite favorable safety profile of oral budesonide over oral hydrocortisone and prednisone, safer agents have been developed for the topical treatment of distal bowel diseases. Budesonide enemas have been investigated for the treatment of acute pouchitis. A prospective, double-blind, double-dummy controlled, 6-week trial of budesonide enema (2 mg/100 mL at bedtime) vs. oral metronidazole (1 g/d) showed that both drugs had a similar efficacy in disease activity, clinical and endoscopic findings. However, adverse effects were observed in 25% of patients in the study group and 57% of patients in the control group.[37]

Oral beclomethasone dipropionate has been studied for the treatment of CARP. In an open-labeled trial of 10 consecutive patients with CARP, investigators gave beclomethasone dipropionate 10 mg/d for 8 weeks. Eight patients (80%) achieved remission and the median total PDAI scores was reduced from 12 (range: 8–14) to 3 (range: 2–9), along with the improvement in IBDQ score.[38]

It appears that corticosteroids may be used in patients with CARP. This author has noticed that the agents are particularly useful in those with IgG4-associated pouchitis[39] or autoimmune pouchitis[40] and in those with CARP who also have concurrent autoimmune disorders, such as PSC and Hashimoto thyroiditis.

Immunomodulators

While immunomodulators, such as azathioprine, 6-mercaptopurine, and methotrexate have been extensively used in the treatment of CD and UC, their use in the treatment of pouchitis, especially in CARP has not been systemically investigated and there are no published studies to date. On the hand, the use of cyclosporin A retention enemas have been described in the treatment of CARP in a case report.[41]

In this author's experience, methotrexate and 6-mercaptopurine may be effective in the maintenance therapy of IgG4-associated pouchitis and autoimmune pouchitis.

Biological therapy

The treatment with anti-tumor-necrosis factor (TNF)α agents has become the standard therapy for moderate to severe CD or UC. There are scant published data on the use of anti-TNF agents in the treatment of pouchitis. An early study of 4 pediatric patients CARP who were treated with infliximab along with an immunomodulator showed significant improvement in symptomatology, endoscopy, and histology. However, 2 of the 4 patients had fistula and one had granulomas on biopsy which raised the question whether those patients had CARP or CD of the pouch.[42] Investigators from University of Toronto reported 42 patients with CARP or CD-like pouchitis who were treated with infliximab and showed an 8-week post-induction response of 74% (48% complete) and sustained 48-week response in 63% (30% complete).[43] In a small open-labeled study of 7 patients with CARP who were treated with 1 year of infliximab, 5 patients had complete clinical response, 1 partial clinical response and 1 no response. Again, 3 of the 5 patients had fistula, raising the diagnostic question of CD of the pouch.[44] In a retrospective, multicenter study of 33 patients with CARP who were treated with infliximab, 21% of patients achieved complete response and 63% had partial clinical response at week 8; 33% and 27% achieved complete response and 33% and 18% showed partial clinical response, at weeks 26 and 52, respectively. There are 13 patients (39%) withdrew treatment with 4 for being lack of efficacy, 4 for losing response, and 5 for side effects.[45]

Adalimumab has also been studied for the treatment of CARP. A retrospective case series of 8 patients with CARP with prior treatment with infliximab showed that adalimumab therapy resulted in 13% of the patients in remission and 62% with a clinical response at week 8; 13% of patients in remission and 38% with a clinical response at week 26, and 4 patients (50%) avoiding a permanent ileostomy at week 52.[46]

In a small case series of 4 patients with antibiotic-refractory and anti-TNF refractory pouchitis, the treatment with vedolizumab, a gut-specific anti-integrin agent, showed a promising outcome.[47] Similarly, alicaforsen, an antisense inhibitor of intercellular adhesion molecule-1 (ICAM-1), has been shown to be effective for the treatment of CARP in case series.[48,49]

Other therapy

Bismuth carbomer liquid enemas have been investigated for the treatment of CARP. In a 3-week trial of 20 patients with