MINIREVIEWS

Infliximab for the treatment of pouchitis

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Abstract

Pouchitis is not a rare complication that develops after an ileal-pouch anastomosis, performed after colectomy in patients refractory to treatment or with complicated ulcerative colitis. This condition may become chronic and unresponsive to medical therapies, including corticosteroids, antibiotics and probiotics. The advent of biological therapies (tumor necrosis factor-α inhibitors) has changed the course of these complications. In particular, in these cases, infliximab (IFX) may represent a safe and effective therapy in order to avoid the subsequent operation for a permanent ileostomy. This article reviews the therapeutic effects of one of the most widely used anti-tumor necrosis factor-α molecules, IFX, for the treatment of complicated pouchitis (refractory to conventional treatment and/or fistulizing).

Core tip: Pouchitis represents the most frequent long term complication of the ileal pouch anal anastomosis and consists of an idiopathic nonspecific inflammation of the ileal mucosa of the pouch. Several studies show the effectiveness of treatment with anti-tumor necrosis factor-α in chronic forms in reducing the synthesis of pro-inflammatory molecules and in restoring the balance between pro-inflammatory and anti-inflammatory cytokines.

INTRODUCTION

Approximately 10% to 30% of patients with ulcerative colitis (UC) refractory to conventional treatment, hemorrhage, perforation, dysplasia or cancer will require surgery[1]. The ileal pouch-anal anastomosis (IPAA) is widely accepted as the procedure of choice for the majority of these patients[2]. This procedure consists of an abdominal colectomy, rectal mucosectomy and construction of an ileal pouch that is anastomosed to the anus. Complications include pelvic sepsis, small bowel obstruction, strictures, incontinence and pouch inflammation[3]. Pouchitis is the most frequent long term complication and is defined as a nonspecific, idiopathic inflammation of the ileal mucosa of the pouch. In fact, the IPAA procedure is associated with pouchitis in approximately 45%-60%[4,5], of whom 60% will suffer from recurrent episodes and 5%-10% will develop chronic pouchitis[5]. This condition was first described by Kock *et al*[6] who noted the inflammation of the continent ileal reservoir. The histopathological changes seen in pouchitis are similar to those seen in UC, with acute inflammation characterized by neutrophil infiltrate, crypt abscesses formation and ulceration[7]. The etiology of pouchitis remains

still unclear. Several risk factors for pouchitis have been investigated, such as extension and severity of UC, backwash ileitis, extraintestinal manifestations, precolectomy thrombocytosis, pANCA positivity, nonsmoking status and nonsteroidal anti-inflammatory drug use. All these factors have still not been demonstrated consistently[8-12]. The increase of interest for this clinical entity is due to its manifestations. Symptoms are generally mild but in severe cases systemic ones may be present.

Infliximab (IFX), a fusion protein dimer of the human tumor necrosis factor-α (TNF-α) receptor (Remicade®, Centocor Incorporated, Horsham, PA, United States), is a chimeric monoclonal antibody to human TNF-α developed as a therapeutic agent to immune-mediated diseases[13]. This drug specifically binds to TNF-α, blocking its biological activity, and has important effects on anergic regulatory T cells, restoring their capacity to inhibit cytokine production[14,15]. IFX has been successfully used for the treatment of inflammatory and fistulizing Crohn's disease (CD), while its role for the treatment of UC remains controversial[16].

The aim of this brief review is to evaluate the importance of treatment with IFX for pouchitis on the basis of a literature review.

IFX AND POUCHITIS

Reports of the incidence of pouchitis vary considerably. The incidence in UC patients varies from 6% to 50% and depends greatly upon the definition and length of follow up[17]. The more important factor is probably the criteria of the definition of pouchitis. According to the literature, pouchitis is defined clinically as episodic or continuous symptoms severe enough to require treatment and the diagnosis has to be confirmed endoscopically[18]. According to this definition, the frequency of pouchitis appears to be highest in the first 6 mo after closure of the ileostomy and then decreases greatly after 12 mo[19].

The cause of pouchitis remains unknown. Several potential mechanisms have been investigated and include fecal stasis, bacterial overgrowth, dysbiosis, genetic susceptibility and immune alteration[20]. However, it is generally accepted that bacterial overgrowth plays an important role and that symptoms and lesions are due to an overproduction of pro-inflammatory cytokines[21]. Of these, TNF-α is maybe the most potent cytokine with direct tissue destructive power.

The treatment of pouchitis is above all empirical and based more on clinical experience than controlled clinical trials. Antibiotics continue to be the main therapy. In fact, most patients respond quickly to metronidazole and/or ciprofloxacin[17]. Chronic pouchitis is more difficult to manage. New promising therapies include probiotics such as VSL#3[22]. The data concerning other therapies are much more limited and include topical (rectal) budesonide[23], oral and topical steroids, topical mesalamine, azathioprine and 6-mercaptopurine[24].

More recently, IFX has been used in these patients.

Results of these studies are summarized in Table 1. Colombel *et al*[25] reviewed 26 patients with an IPAA and CD-related complications treated with IFX. The median time between the IPAA and the diagnosis of CD was 4.5 years (range 0.1-16 years). The main reasons for changing the original UC diagnosis to CD were complex: perianal or pouch fistulizing disease in 14 patients (54%), pre-pouch ileitis in five (19%), and both pre-pouch ileitis and complex fistula in seven (27%). Patients received one to three doses of IFX over 8 wk as induction therapy. Subsequently the patients received a variable number of maintenance infusions. At a short term follow up, 16/26 patients (62%) had a complete response, 6 of 26 (23%) had a partial response, and 4 of 26 (15%) had no response. Information regarding long term follow up was available in 24 patients. After a median follow up of 21.5 mo (range 3-44 mo), 8 patients (33%) either had their pouch resected or had a persistent diverting ileostomy. The pouch was functional in 16/24 (67%) patients, with either good (*n* = 7) or acceptable (*n* = 7) clinical results in 14/24 (58%). Of these 14 patients, 11 were under long term, on demand, or systematic maintenance treatment with IFX. The authors conclude that IFX is beneficial in both the short and long-term treatment of patients with an IPAA performed for a presumed diagnosis of UC who subsequently develop CD-related complications.

Viscido *et al*[26] evaluated the efficacy of IFX in the treatment of chronic refractory pouchitis complicated by fistulae following IPAA for UC. Seven patients (4 females, 3 males) with chronic refractory pouchitis complicated by fistulae were included in the study. Pouchitis was diagnosed by clinical, endoscopic and histological criteria. The sites of the fistulae were as follows: pouch-bladder in one, vaginal in three, perianal in two, and both vaginal and perianal in one. Extra-intestinal manifestations (erythema nodosum, arthralgia) were present in 4 patients. CD was carefully excluded in all patients after re-evaluation of the history, re-examination of the original proctocolectomy specimen and examination of the proximal small bowel. All patients had been treated with antibiotics and three with steroids. Patients received IFX, 5 mg/kg, at 0, 2 and 6 wk. Azathioprine (2.5 mg/kg) was also started for all patients as bridge therapy. Clinical response was classified as complete, partial or no response. Fistulae closure was classified as complete (cessation of fistulae drainage and total closure of all fistulae), partial (a reduction in the number, size, drainage or discomfort associated with fistulae) or no closure. The pouchitis disease activity index and quality of life were also used as outcome measures. Clinically, all patients improved. After a follow up of 10 wk, 6 of the 7 patients had a complete clinical response and five had complete fistulae closure. Moreover, the median pouchitis disease activity index decreased from 12 (baseline) (range 10-15) to 5 (range 3-8); the median quality of life decreased from 37 points (range 33-40) to 14 (range 9-18). Erythema nodosum and arthralgia showed complete remission soon after the first infusion of IFX. These preliminary

Table 1 Studies analyzing the use of infliximab in pouchitis

Ref.	Number of patients	Fistulae	Extraintestinal manifestations
Colombel et al[25]	26		
Viscido et al[26]	7	Perianal (2), vaginal (3), perianal-vaginal (1) pouch-bladder (1)	Arthralgia (3), erythema nodosum (3)
Kooros et al[27]	4	Perianal (2)	
Molnar et al[28]	1	Perianal (1)	Pyoderma gangrenosum
Semb et al[30]	3	Not specific (3)	-
Calabrese et al[31]	10	-	-
Yeates et al[29]	1	-	-
Ferrante et al[32]	28	Perianal (2), vaginal (5)	Not specific (11)
Barreiros-de Acosta et al[33]	33	Not specific (10)	Not specific (12)
Barreiros-de Acosta et al[34]	8	Not specific (7)	-
Viazis et al[35]	7	Perianal (2), pouch-bladder (1)	Arthralgia (2), Erythema nodosum (2)

results indicate that IFX may be recommended for the treatment of refractory pouchitis complicated by fistulae following IPAA for UC.

IFX has been also used in paediatric patients with CD and IPAA. In a retrospective review, Kooros *et al*[27] studied patients originally diagnosed with UC who developed findings compatible with CD. Refractory pouchitis developed in all patients as well as protracted symptoms of diarrhea, abdominal pain, joint pain and incontinence. All patients received IFX. Four pediatric patients (2 males and 2 females) with mean age of 14.5 years (range 11-18 years) were studied. The development of perianal fistulas in 2 patients, granuloma on biopsy in 1 patient and perianal skin tag in 1 patient, led to a diagnosis change of CD. After failure to respond to antibiotics, aminosalicylates and immunomodulators such as azathioprine and 6-mercaptopurine, all patients were treated with IFX. Patients received IFX infusions at a dose of 5 mg/kg, initially at week 0, 2 and 6 and subsequently at 8 wk intervals in combination with an immunomodulator drug. All patients showed marked improvement clinically, endoscopically and histologically. The authors conclude that IFX can be used successfully for the treatment of pediatric patients with CD and IPAA who are refractory to conventional therapies.

In the literature we found other two pediatric cases. A 14-year-old girl with fistulising pouchitis (perianal fistula) associated with pyoderma gangrenosum and another young girl, 8-year-old, with refractory pouchitis, both treated successfully with IFX[28,29].

Semb *et al*[30] reported the use of IFX in three patients who developed pouch-related fistula after undergoing IPAA surgery for UC.

Calabrese *et al*[31] evaluated the efficacy of IFX in treatment of chronic refractory pouchitis complicated by ileitis using a wireless capsule endoscopy (WCE). Ileitis was documented using WCE and pouchitis was diagnosed by clinical, endoscopic and histological criteria. Sixteen patients with chronic refractory pouchitis complicated by ileitis were enrolled. CD and intestinal infections were excluded in all patients. Patients were treated with IFX and WCE was repeated at week 10. Ten patients completed the study and clinical remission was achieved in nine patients. At WCE and pouch endoscopy, a com-

plete recovery of lesions was observed in 8 patients. One patient presented with four small lesions of the ileum at the 6th week of treatment and 1 patient did not show any modification. Clinical and endoscopic remission was maintained in these eight patients for at least 6 mo. The authors concluded that IFX may be recommended for the treatment of chronic refractory pouchitis complicated by ileitis[31].

Ferrante *et al*[32] studied 28 IPAA patients who received IFX for refractory luminal inflammation (pouchitis and/or pre-pouch ileitis, *n* = 25) and/or pouch fistula (*n* = 7). At week 10 following the start of IFX, 88% of patients with refractory luminal inflammation showed clinical response (14 partial, 8 complete), while 6 patients (86%) showed fistula response (3 partial, 3 complete). The modified pouchitis disease activity index (mPDAI) dropped significantly from 9.0 to 4.5 points (P < 0.001). After a median follow up of 20 mo (7-36 mo), 56% showed sustained clinical response while 3 out of 7 fistula patients showed sustained fistula response. Five patients needed permanent ileostomy[32].

Barreiro-de Acosta *et al*[33], in a retrospective, multicenter study, studied 33 patients with chronic refractory pouchitis treated with IFX (5 mg/kg). Short term IFX efficacy was evaluated at week 8 and mid-term efficacy at week 26 and 52. Complete response was defined as cessation of diarrhea and urgency and partial response as marked clinical improvement but persisting symptoms. The mPDAI without endoscopy was calculated when available. Thirty-three consecutive UC patients with chronic refractory pouchitis were included (18 male, mean age 45 years, range 21-67 years). At week 8, 21% of patients achieved complete response and 63% showed partial clinical response. At weeks 26 and 52, 33% and 27% achieved complete response and 33% and 18% showed partial clinical response, respectively. Thirteen patients (39%) withdrew from treatment (4 for lack of efficacy, 4 for loss of response and 5 for adverse events). None of the potential factors analyzed had an influence on response to IFX.

More recently, Barreiro-de Acosta *et al*[34] analysed the use of adalimumab, a fully human monoclonal antibody to TNF-α (Humira®, Abbott Laboratories, Abbott Park, IL), in 8 chronic refractory pouchitis

previously treated with IFX. After 8 wk, 13% of the patients achieved remission and 62% showed a clinical response. At week 26, 13% achieved remission and 38% showed a clinical response. At 52 wk, 50% of the patients avoided a permanent ileostomy but only 25% achieved remission. The authors concluded that adalimumab may be an alternative for these patients who have chronic refractory pouchitis previously treated with IFX[32].

Finally, Viazis *et al*[35] evaluated the long term benefits of one year administration of IFX in patients with chronic refractory pouchitis following IPAA for UC. Seven patients were included in the study and received IFX 5 mg/kg at 0, 2, 6 wk and thereafter every 2 mo for 1 year. Three patients had fistulae (1 pouch-bladder, 2 perianal) and 4 extraintestinal manifestations (2 erythema nodosum, 2 arthralgia). CD was excluded after re-evaluation of the history and small bowel examination with enteroclysis or capsule endoscopy. All patients were refractory to antibiotics and 3 to azathioprine. Clinical response was classified as complete, partial and no response. Fistulae closure was classified as complete, partial and no closure. The pouchitis disease activity index (PDAI) was used as an outcome measure. All patients were followed up for 3 years after discontinuation of IFX therapy. After 1 year of IFX administration, 5 patients had complete clinical response, 1 partial clinical response and 1 no response, while 2 out of the 3 patients with fistulae had a complete closure. The median PDAI dropped from 11 (baseline) (range 10-14) to 5 (range 3-8). Extraintestinal manifestations were in complete remission too. Three years after completion of therapy, all patients with complete clinical response at one year remained in remission[35].

CONCLUSION

Pouchitis is an idiopathic inflammatory condition of the ileal reservoir in patients who have undergone a proctocolectomy. Ileal pouch-anal anastomosis has become the surgical treatment of choice. A subset of patients with ileal pouches can develop CD or a Crohn's-like condition of the ileal pouch after surgery. Diagnosis, differential diagnosis and management of CD of the ileal pouch have been challenging.

An overlap with UC is suggested by the frequency with which pouchitis affects patients with UC compared with familial adenomatous polyposis patients[8]. There is significant clinical evidence implicating bacteria in the pathogenesis of pouchitis. Studies using culture and molecular methods demonstrate a dysbiosis of the pouch microbiota in pouchitis. Risk factors, genetic associations and serological markers of pouchitis suggest that the interactions between the host immune responses and the pouch microbiota underlie the etiology of this idiopathic inflammatory condition[8]. Evidence suggests that pouchitis could result from a reactivation

of the immunological mechanisms that lead to UC. In these conditions, it has been observed that the ileal-pouch mucosa synthesizes a variety of pro-inflammatory molecules, including TNF-α, with an imbalance between pro-inflammatory and anti-inflammatory cytokines[36-38]. Furthermore, patients who develop pouchitis show greatly increased levels of signal transducer and activator of transcription-1 (STAT1) activation in the pouch mucosa[11]. STAT1 is a pro-inflammatory transcription factor similar to nuclear factor kappa B, which activates genes involved in inflammatory and immunological responses[39].

Early recognition of this condition is very important for treatment. Although most of these patients show a good response to antibiotic therapy, there are a few cases in which other therapeutic options, such as topical and/or oral mesalamine, topical and/or oral steroids, and immunosuppressive and biological treatment, have to be used. The advent of biological response modifiers (anti-TNF-α inhibitors) represents a new and efficacious approach that is able to modify the clinical course of such patients.

Reading the literature, we found several studies included in this brief review that show for the first time that IFX may significantly contribute to the salvage of complicated pouchitis in patients after IPAA, both in patients with a diagnosis of UC and CD. In our opinion, the decision should be individualized, even if the administration of IFX seems to be safe in both short and long term treatment, and also in paediatric patients.

In conclusion, since the introduction of the biological agents, antibodies to cytokine TNF-α, the treatment of complicated pouchitis refractory to conventional treatment and/or fistulizing, has changed dramatically.

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