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Use of Biologics in Pouchitis – A Systematic Review

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Abstract

Data about the effectiveness of biologics, including anti-TNF therapy and anti-integrin strategies, in antibiotic refractory pouchitis or Crohn's disease-associated pouch complications are sparse. We performed a systematic review of the literature in Medline and Web of Science. All English language publications and meeting abstracts describing patients with pouchitis treated with anti-TNF or anti-integrin therapies were included. We identified a total of 17 papers and 2 abstracts, most of these retrospective case series, including a total of 192 patients treated either with infliximab (IFX; n=140) or adalimumab (ADA; n=52). No reports were found for anti-integrin therapies or other anti-TNF agents such as certolizumab pegol or golimumab. Due to the heterogeneity of the studies, small numbers of patients, differing co-treatments and subjective outcome definitions, the exact efficacy of these biologic therapies cannot be assessed in a combined fashion. Overall IFX appears to have good clinical effectiveness in selected patients achieving up to 80% short and around 50% long-term response, whereas the few data available for ADA are not sufficient to draw valid conclusions. Larger prospectively collected multi-center data with clearly defined inclusion criteria and outcomes are necessary to better define the clinical value of anti-TNF therapy in patients with antibiotic refractory pouchitis or Crohn's-like complications of the pouch.

Keywords

pouchitis; inflammatory bowel disease; anti-TNF therapy; biologics; infliximab; adalimumab

Introduction

Ulcerative colitis (UC) affects approximately 500,000 Americans, most of whom are young adults (20 – 40 years); although the disease may present at a very early age (5–10 years) or later in life (>60 years).[1–3] The inflammatory process in UC can be primarily localized to the rectum (proctitis) or can extend proximally in a contiguous manner involving the mucosa up to the splenic flexure (left sided colitis) or can involve the entire colon (extensive colitis). The key clinical feature of UC is bloody diarrhea. Due to a refractory course of UC or histologically proven dysplasia, approximately 20–35% of patients with UC eventually

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undergo colectomy.[4–6] This surgery is most often performed in conjunction with an ileal pouch-anal anastomosis (IPAA). The ileal pouch serves as a reservoir for the stool and improves functional outcomes following colectomy. Pouchitis is the most common long-term complication after IPAA affecting up to 70% of patients following colectomy for UC.[7–11] The clinical symptoms can include diarrhea, urgency, crampy abdominal pain, fever, bloody bowel movements, dehydration, as well as extraintestinal manifestations such as joint pain.[12, 13]

The pathogenesis of pouchitis remains only incompletely elucidated.[14–16] Currently, the most favored underlying pathomechanisms of pouchitis are a) dysbiosis of the bacterial flora of the pouch and/or b) dysregulation of the mucosal inflammatory responses in genetically susceptible patients (see rationale for using biologics). In addition, bile acid toxicity, ischemia and ongoing infection may contribute in some patients to the clinical and endoscopic picture of pouchitis.[17] A role of the bacterial flora in the pathogenesis of pouchitis has been strongly suggested by clinical trials demonstrating significant clinical effectiveness of antibiotics (e.g. ciprofloxacin, metronidazole) to treat pouchitis. Several analyses describe bacterial dysbiosis present in patients with pouchitis.[14, 18–20] Studies comparing the bacterial flora of pouches of patients with familial adenomatous polyposis (FAP), who rarely develop pouchitis after colectomy, with patients with IPAA and a prior history of UC, have found sulfate reducing bacteria in the majority of UC patients but none in FAP patients.[21]

Conventional therapeutic approaches for pouchitis

Different antibiotic therapies including ciprofloxacin, metronidazole and rifaximin have been shown to treat pouchitis in the majority of patients.[22–26] The probiotic VSL#3, which is a highly concentrated bacterial cocktail of 8 different bacterial species, prevents acute and chronic pouchitis, but is only effective in a subgroup of patients.[27–32] Agents known to be efficacious in UC including budesonide enemas, mesalamine enemas and suppositories have all been used with some success in treating pouch inflammation.[33–35] Uncontrolled observations also report some efficacy of oral sulfasalazine or oral bismuth subsalicylate as well as butyrate and glutamine suppositories.[36–38] More recently porous carbon microspheres (AST 120) have been investigated in patients with chronic pouchitis.[39] Initial results were promising but a confirmation by a larger placebo controlled trial is necessary. Allopurinol, inulin and bismuth carboner foam enemas were also explored without significant clinical efficacy.[40–42]

Rationale for Biologics

Whereas many patients respond to antibiotic therapy, various data also point towards the option of an immunosuppressive or immunmodulating approach using biologics such as anti-TNF agents. The role of an aberrant regulation of the mucosal immune system is underscored by the fact that pouchitis rarely occurs in patients with familial adenomatosis coli (FAP), who underwent an indentical surgery of colectomy with IPAA.[43] Similar to Crohn's disease and UC, there are known genetic or genetically influenced risk factors for the development of pouchitis, which are associated with a dysregulation of the mucosal

immune system. Some of these risk factors include the presence of antineutrophil cytoplasmatic antibody with perinuclear staining pattern (pANCA), a history of primary sclerosing cholangitis (PSC) as well as an association of known IBD risk genes such as CARD15.[44] Interestingly, corresponding upregulation of several proinflammatory genes in patients with pouchitis has been described in the endoscopically and histologically normal mucosa in the afferent limb of the pouch suggesting that pouchitis may represent not a locally restricted but rather a more systemic disease.[45] It is estimated that about 3–10% of patients with prior colectomy and IPAA, with an original diagnosis of UC, can eventually develop either verified de novo Crohn's disease with findings of granulomas on histology or are diagnosed with a Crohn's- like disease.[46, 47] This disease entity is clinically and endoscopically defined as findings of severe inflammatory pouchitis, which is typically refractory to antibiotic treatment, or stricturing inflammation of the afferent limb or fistulizing disease involving the pouch, the perineum or the small bowel. Patients with Crohn's disease of the pouch or Crohn's-like complications have a significantly increased risk for pouch failure.[48] Therefore, especially in this patient group, an aggressive therapeutic approach is warranted.

We performed a systematic review of the literature to explore the efficacy of biologics, particularly of anti-TNF therapies in patients with IPAA and pouch-associated complications, such as chronic pouchitis or pouch-associated fistulizing disease, to evaluate the efficacy of such an approach.

Methods

To identify relevant articles and abstracts, a systematic literature search was performed using both medical subject headings (MESH) and keywords. The following terms were used: "pouchitis", "infliximab", "adalimumab", "golimumab", "certolizumab", "natalizumab", "vedolizumab". The search was restricted to English language publications involving humans and was performed in the following databases: MEDLINE (1966 to February 2015), Web of Science (for meeting abstracts) and Clinical trials database (ClinicalTrials.gov). The keywords were linked by the Boolean operators (and, or) to refine the search. Data from full papers and meeting abstracts were extracted. Additional efforts to identify relevant trials were made through review of reference lists of included articles. Meeting abstracts, which were later published as a full paper, were not included as duplicates.

Treatment of pouchitis with infliximab (IFX) or adalimumab (ADA)

Large prospective trials investigating the role of anti-TNF therapy in patients with antibiotic refractory pouchitis or Crohn's-like complications such as fistulizing or stricturing diseases are lacking. Combining all available data, treatment outcomes are reported in 19 publications (including 2 abstracts) for 192 patients (140 treated with infliximab (IFX) and 52 with adalimumab (ADA) (see tables 2 and 3).[46, 49–66] Most studies are retrospectively analyzed case series or single patient outcomes. Indications for anti-TNF therapy are listed in table 1. In some studies patients with stricturing and or fistulizing pouch complications were also re-characterized as Crohn's disease or Crohn's-like disease.

Described treatment regimens are IFX or ADA monotherapy; however, particularly in the case of IFX, therapy additionally occurred in combination with azathioprine/6-mercaptopurine, steroids or methotrexate. Within the total reported 140 IFX-treated patients, the three largest IFX studies comprising 87 patients (62%), only 23% of patients were treated with IFX monotherapy, 71% with a combination of IFX and azathioprine or 6-mercaptopurine and 6% with IFX and methotrexate.[50, 52, 53] The two largest ADA reports combine a total of 51 patients (98% of all reported patients treated with ADA). [49, 54] Li et al. portray data from a single center in the USA (Cleveland; 17 previously reported patients by Shen et al[55] were incorporated in this report) and Barreiros-de Acosta et al. describe outcomes in the setting of a retrospective multicenter study in Spain. The majority of patients in both studies (86%) were treated with monotherapy and 14% with the addition of azathioprine.

Regarding other co-treatments, several studies also describe continuation of antibiotics, steroids or mesalamine despite previous failure of these therapeutic approaches.[49, 50, 52, 54] In the studies by Colombel et al. and Li et al., additional endoscopic (e.g. balloon dilation) and/or surgical procedures (fistulotomies) were performed in subgroups of patients, which most likely positively affected the outcome.[52, 54]

Since the studies did not define standardized treatment approaches, it is difficult to firmly state the overall efficacy of anti-TNF therapy. Additionally, the reports describe a mixed population of patients with antibiotic resistant pouchitis or Crohn's-like complications (stricturing or fistulizing disease) and the outcome criteria were often defined by subjective physician assessed improvement such as partial or complete response.

Based on the 3 largest retrospective analyses with a total of 87 patients with pouchitis and/or pre-pouch ileitis or fistulizing pouch complications, the combined partial and complete response after 6–10 weeks of IFX therapy is around 84%–88% (table 2).[50, 52, 53] For long-term outcomes of IFX therapy (52 weeks or up to median follow-up of 21–22 months), the combined partial and complete response rates are 45% –58%. Failure rates for IFX with loss of pouch and consecutive ileostomy are reported between 12% –33%. Two of the 3 studies also reported the treatment success of fistulizing disease with complete fistula closure in 43% –50% of the patients (n=28).[52, 53]

The efficacy of ADA is described in 48 patients at the Cleveland Clinic with a short and long term combined partial and complete response of 71% and 54%; respectively. However; the median follow-up was just 25 weeks (table 2).[54] One strength of this study is the separate evaluation of outcomes based on the different types of complication behavior (inflammatory, fibrostenotic or fistulizing behavior; table 2). The only other ADA-pouchitis study (aside of a single case report), a retrospective multi-center Spanish case series of 8 patients, included only patients with previous IFX therapy, which was discontinued either due to adverse events or due to a loss of response (table 3).[49] In the Cleveland Clinic series only 6 of the 48 patients (12.5%) had been previously treated with IFX. The dissimilar patient population in both studies aside, the longer follow up of 52 weeks in the Spanish study, and diverse concomitant treatment approaches (e.g. 46% of the patients at the Cleveland Clinic underwent additional interventional endoscopic therapies) might explain

the different results. The high failures rates of 50% described in the Spanish report and remission rates of only 25% were likely influenced by the fact that all patients had previously failed infliximab.

Adverse events of anti-TNF therapy in pouchitis

Reported adverse events in the setting of anti-TNF therapy were mainly infusion reactions (IFX) or infusion site reaction (ADA). Thus, the adverse event profile of mono anti-TNF therapy or combination therapy with an immunosuppressant such as azathioprine/6-mercaptopuirne seems to be similar to the profile described for Crohn's disease or ulcerative colitis.[67] All studies listed in table 2 and 3 do not state any specific pouch related side effect, which could be attributable to potential differences in the pathophysiology of pouchitis compared to Crohn's disease or ulcerative colitis.

Treatment of pouchitis with other biologics

As of early 2015 there are no published reports or abstracts available describing the efficacy of certolizumab or golimumab in patients with antibiotic refractory pouchitis or fistulizing and/or stricturing pouch complications. Similarly, reports about therapy of refractory pouchitis with natalizimab or vedolizumab are lacking.

Summary and Conclusion

Well-controlled studies of anti-TNF therapy in antibiotic resistant or fistulizing and/or stricturing pouchitis are at present unavailable. A coherent evaluation of the efficacy of anti-TNF therapy using data gathered from published studies is difficult due to the heterogeneity of patients, co-treatments and outcome parameters. Furthermore, there are no existing data describing the efficacy of biologics in treating cuffitis, which alone can be a potential trigger for recurrent pouchitis. However, the available data for IFX suggest clinical effectiveness in treating antibiotic refractory or fistulizing pouchitis. The data for ADA are much more limited and sufficient long-term outcomes are lacking. Given the relatively small number of patients with complicated pouchitis, it is unlikely that industry-sponsored, placebo controlled studies will evaluate the effectiveness of biological therapies in the near future. Therefore, multi-center prospective registries, including distinctly defined pouchitis patients and well-defined objective common endpoints, should be initiated to study the effectiveness of biologics in these sub-groups of patients with complicated pouchitis.

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Table 1

Indications for biologics in patients with IPAA

- Antibiotic refractory pouchitis
- Fistulizing complications after IPAA
- Inflammatory stricturing pouchitis

Table 2

Anti-TNF therapy in patients with pouchitis, case reports, case series and cohort studies with ≥ 10 patients

Author/ Year	Design	n	Drugs	Indication for therapy	Outcome/ Follow-up	Outcome measures	Outcome
Colombel 2003[52]	Retrospective; single center	26[a]	IFX + AZA/6-MP (n=24; IFX + MTX (n=2)	Pre-pouch ileitis (n=5); pre-pouch ileitis + fistula (n=7); pouchitis + fistula (n=14)	Short term: Induction therapy with IFX Long term: Median 22 months	Clin.assess.	Short term (n=26): Complete response: 16/26 (62%). Partial response: 6/25 (23%). No response: 4/26 (15%). Fistula outcome(n=21): 3 patients setton placement + IFX Fistula closure 9/18 (50%). Long term (n=24): Remission 7/24 (29%). Partial response 7/24 (29%). Loss of response 2/24 (8%). Ileostomy and or pouch resection 8/24 (33%).
Calabrese 2008[51]	Single-blind, prospective, single center	10	IFX (only 3 infusions)	Pouchitis refractory to antibiotics > 4 weeks and lesions in jejunum-ileum on capsule endoscopy (WCE)	Week 10 6 months	WCE week 0 and 10; PDAI Clin.assess.	Capsule endoscopy week 10 (n=10): 8/10 (80%) complete resolution of small bowel lesions. 1/10 (10%) improvement of small bowel lesions. 1/10 (10%) no response. PDAI (n=10): 13 (11–16) drop to 5 (3–8) Median stool frequency (n=10): 9(7–11) to 4 (3–6) 6 months: All patients with endoscopic resolution (n=8) still in remission at 6 months.
Shen 2009[55]	Retrospective analysis of prospectively collected data; single center.	17	ADA	CD of pouch phenotype: inflammatory (n=10), fibrostenotic (n=2); fistulizing (n=5)	4 weeks and 8 weeks	Clin.assess. PDAI	Week 4 (n=17): Complete response: 7/17 (41%) Partial response: 6/17 (35%) No response: 4/17 (24%). Outcome fistula week 4: Fistula closure: 1/5 (20%). Reduction of fistula drainage: 1/5 (20%). Significant decrease of symptom, endoscopy, afferent limb, cuff and global assessment PDAI score ($p<0.05$). Week 8: Complete response: 8/17 (47%). Partial response: 4/17 (24%). No response: 5/17 (29%). 5 patients also underwent endoscopic procedures. Pouch failure: 3/17 (18%).
Ferrante 2010[53]	Retrospective; multicenter	28	IFX (n=5) IFX +AZA n=20 IFX + MTX n=3	Pouchitis including pre-pouch ileitis refractory to antibiotics > 4 weeks (n=21) + additional fistula	Short term: 10 weeks Long term: Median 21 months	Clin.assess. mPDAI if available	Short term (n=25): Complete response: 8/32 (32%). Partial response: 14/32 (56%). No response: 3/25 (12%). Short term fistulae (n=7): Complete response 3/7 (43%).

Author/ Year	Design	n	Drugs	Indication for therapy	Outcome/ Follow-up	Outcome measures	Outcome
				(n=4) or fistula alone (n=3)			Partial response 3/7 (43%). No response 1/7 (14%). mPDAI (available in n=18): median drop from 9 to 4.5; p<0.001. Long term (n=25): Sustained clinical response: 13/25 (52%). Loss of response: 6/25 (27%). Delayed hypersensitivity: 2/25 (10%). Primary no response 3/25 (12%). Switch to azathioprine 1/25 (4%). Overall pouch failure and ileostomy: 5/25 (20%).
Haveran 2011[46]	Retrospective; single center	13	IFX (n=4) IFX +AZA (n=9)	CD -like pouch complications: Stricturing pouchitis (n=1) Fistulizing pouchitis (n= 12)	Mean follow –up: 38+/- 9 months	Clin.assess.	Complete resolution or significant improvement (n=13): Fistulizing disease (n=12): 6/12 (50%). Stricturing disease (n=1): 1/1 (100%). Failed therapy and stoma: 6/13 (46%).
Barreiros-de Acosta 2012[50]	Retrospective; multi-center	33	IFX (n=15) IFX+ AZA (n=18)	Antibiotic refractory pouchitis (4 weeks). 10/33 (30%) with additional pouch associated fistula	Week 8, 26, 52	Clin.assess.; modified PDAI (if captured)	Complete, partial and no response: Week 8: 7/33 (21%); 21/33 (63%); 5/33 (15%). Week 26: 11/33 (33%); 11/33 (33%); 11/33 (33%). Week 52: 9/33 (27%); 6/33 (18%); 18/33 (55%). 13/33 (39%) withdrew dew to lack of response, loss of response or adverse events. mPDAI shows concomitant improvement with IFX in patients with pouchoscopies performed. Outcome of patients with fistulae not reported. Failed therapy and stoma: 4/33 (12%).
Li 2012[54]	Retrospective analysis of prospectively collected data	48[b]	ADA n=43 ADA + 6-MP/AZA: n=5 ADA + steroids n=18 Other[c]	CD of pouch: Inflammatory behavior (n=15) Fibrostenotic behavior (n=8) Fistulizing behavior (n=25)	Short term: Median 8 weeks Long term: Median 25 weeks	Clin.assess. PDAI	Short term (n=48) Complete response: 24/48 (50%). Partial response: 10/48 (21%). No response: 14/48 (29%). Long term (n=48): Complete response: 16/48 (33%). Partial response: 10/48 (21%). No response: 22/48 (46%). Clinical response according to behavior subtypes: Inflammatory or fibrostenotic disease (n=23): Short term: Complete response: 10/23 (44%). Partial response 6/23 (26%). No response 7/23 (30%). Long term: Complete response: 7/23 (30%). Partial response: 4/23 (17%). No response: 12/23 (52%). Fistulizing disease: Short term: Complete response: 14/25 (56%). Partial response: 4/25: (16%). No response: 7/25 (28%). Long term:

Author/ Year	Design	n	Drugs	Indication for therapy	Outcome/ Follow-up	Outcome measures	Outcome
							Complete response: 9/25 (36%). Partial response: 6/25 (24%). No response: 10/25 (40%). Mucosal healing: Short term: 20/48 (42%). Long term: 13/48 (27%).

[a] The outcome of 7 of the 26 patients was previously reported by Ricart 1999 (table xx).[62]

[b] 17 patients from a previous study from the same center (Shen 2009) were included in this analysis

[c] Additional endoscopic therapy in 22/48 (46% patients (Balloon dilation, needle knife therapy); 6 patients treated previously with IFX (12.5%; 3 with history of infusion reaction and 3 with either no response or loss of response).

Clin.assess.; Clinical assessment: no predefined score was utilized. Success or partial success are derived from patient reported outcomes (e.g improvement of abdominal pain, bleeding and diarrhea frequency, reduction of fistula drainage) and physician assessments (e.g fistula closure); PDAI; pouch disease activity index [68]; mPDAI; modified pouch index [69]

Table 3

Anti-TNF therapy in patients with pouchitis, case reports, case series and cohort studies with < 10 patients[a]

Author/ Year	Design	n	Drug	Indication for therapy	Outcome/ Follow-up	Outcome measures	Outcome
Ricart 1999[62]	Retrospective; single center	7	IFX (n=2) + AZA (n=4) or MTX (n=1),	CD and IPAA with perianal or pouch vaginal fistula (n=5) or pre-pouch ileitis with granuloma on histology (n=2)		Clin. Ass.	Complete response: 6/7 (86%). Partial response: 1/7 (14%). Fistulae: 4/5 (80%) closure of fistula.
Viscido 2003[65]	Prospective	7	IFX + AZA	Antibiotic refractory pouchitis (4 months) + Fistulae	Short term: 10 weeks Long term 11 months (range 7-33 months)	Clin.assess. PDAI	Short term: Complete response: 6/7 (86%) Partial response: 1/7 Fistulae: 5/7 (71%) fistula closure. Long term: Clinical response 7/7 (100%). Short term: PDAI mean 12 (10–15) decrease to 5 (3–8)
Kooros 2004[59]	Case series single center	4	IFX + AZA (n=3) or steroids (n=1)	Fistula (n=2), histogy granuloma n=1), perianal skin tag (n=1)	ND	PCDAI PDAI	All patients improved clinically and endoscopically.
Mohanty 2004[60#]	Case series single center	8	IFX	Pouchitis	ND	Clin.assess.	Complete response: 7/8 (88%). Partial response 1/8 (12%).
Molnar 2008[61]	Case study	1	IFX	Antibiotic resistant pouchitis, pyoderma	16 months	Clin.assess. PDAI	Clinical and endoscopic remission.
Yeats 2010[66]	Case study	1	IFX	Antibiotic and 6-MP refractory pouchitis	36 months	Clin.ass. Endoscopy	Clinical and endoscopic remission.
Akitake 2010[56]	Case study	1	IFX	Pouchitis + enteritis	ND	Clin.assess. + endoscopy	Remission.
Barreiros-de Acosta 2012[49]	Retrospective, Multi-center	8[b]	ADA; 5 monothe rapy, 3 +AZA	Chronic antibiotic refractory (4 weeks) pouchitis	1 year	Clin.assess. and if available PDAI	Week 8: Remission: 1/8 (13%). Response: 5/8 (63%). No response: 2/8 (25%). Week 52: Remission: 2/8 (25%). Response: 2/8 (25%). No response: 2/8 (50%).

Author/ Year	Design	n	Drug	Indication for therapy	Outcome/ Follow-up	Outcome measures	Outcome
Viazis 2011[64]	Prospective cohort, single center	7	IFX	Chronic antibiotic refractory (4 weeks); n=4; fistula (n=3)	1 year	PDAI + Clin.assess.	Complete response: 5/7 (71%). Partial response: 1/7 (14%). No response: 1/7 (14%). Fistula closure: 2/3 (67%).
Viazis 2013[63]	Prospective cohort, single center	7[c]	IFX	Chronic antibiotic refractory (4 weeks); n=4; fistula (n=3)	3 years	Clin.assess.	6/7 (86%) ongoing complete response.
Alvarez 2014[57#]	Case study	1	ADA	Collagenous pouchitis	ND	Clin.assess.	Improvement and resolution of collagen layer
Iizuka 2014[58]	Case study	1	IFX	Chronic antibiotic refractory+ fistula	12 months	Clin.assess. PDAI	Remission, recurrence of symptoms while off IFX, then again remission after restart IFX

[a] Only English language articles were included in this systematic review. A Danish language case series of 3 patients with pouchitis and fistulizing complications treated with IFX was published in 2008[70]

[b] All patients had been previously treated with IFX; in five cases IFX was discontinued due to adverse events, in three cases because of a loss of response.

[c] Same patients as in Viazis 2011 but longer follow-up

[#] meeting abstract

Clin.assess.; Clinical assessment: no predefined score was utilized. Success or partial success are derived from patient reported outcomes (e.g improvement of abdominal pain, bleeding and diarrhea frequency, reduction of fistula drainage) and physician assessments (e.g fistula closure);PDAI; pouch disease activity index[68];PCDAI; pediatric Crohn's activity index.[71]