International Journal of Surgery 65 (2019) 80–85

Contents lists available at ScienceDirect

International Journal of Surgery

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

Original Research

# Preoperative exposure to anti-tumor necrosis factor therapy in ulcerative colitis patients undergoing ileal pouch-anal anastomosis (IPAA) is not associated with histological fibrosis: A case control study

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A B S T R A C T

*Background:* We sought to determine whether preoperative exposure to anti-TNF therapy affects objective histological measures of fibrosis in the colorectum.
*Methods:* Ulcerative colitis (UC) patients who received infliximab as maintenance therapy pre IPAA surgery were identified and compared to anti-TNF-naïve matched controls by age, sex, BMI, disease duration, albumin levels, and post-operative leak outcome. Hematoxylin and eosin- (H&E) and trichrome-stained slides from the most distal, well-oriented, full-thickness section of colorectum from each patient's total colectomy specimen were evaluated. Blinded histopathological assessment of the degree of fibrosis was performed using a semi-quantitative pictorial scale.
*Results:* Histological fibrosis in 65 patients from the therapy group was compared to 65 patients from the matched control group. There were no statistically significant differences in the degree of fibrosis observed in any of the bowel layers. In the lamina propria, 29% of the control group and 28% of the treatment group had fibrosis scores ≥3. Fibrosis scores were higher in the submucosa, with both groups having 66% of patients showing scores ≥3. Similarly, in the region above the muscularis propria, 77% of the control group and 80% of the treatment group had fibrosis scores ≥3. In the subserosa, fibrosis scores were lower, with 25% of the control group and 32% of the treatment group having fibrosis scores ≥3.
*Conclusion:* Resection specimens from UC patients treated with maintenance anti-TNF therapy who underwent IPAA surgery showed no significant differences in the degree of histologic fibrosis in any of the bowel layers compared to a matched control group.

## 1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD), are idiopathic, chronic intestinal conditions characterized by periods of remission and relapses which are typically unpredictable and without clear inciting factors [1]. Ulcerative colitis primarily affects the colon and rectum. Numerous studies have shown that up to 20% of UC patients will require surgical intervention at some point in their disease course [2–4]. Surgery is traditionally recommended in the setting of fulminant UC, as treatment for refractory UC, and/or for management of colorectal dysplasia [5,6]. Ileal pouch-anal anastomosis (IPAA) surgery is a reconstructive solution for patients following proctocolectomy that allows for the avoidance of a permanent ileostomy [7–9].

Anti-TNF therapy, such as Infliximab (IFX), was introduced in treatment algorithms for UC more than a decade ago and has been shown to be an effective treatment option for patients with moderate to severe UC who have failed conventional treatments and for patients with steroid-dependent disease [10–12]. However, there is ongoing debate regarding the effect of anti-TNF therapy on post-operative outcomes following IPAA surgery. Some have reported that the preoperative administration of anti-TNF agents increases the rates of postoperative leaks and septic complications [13], while others found that preoperative exposure to anti-TNF therapy is not associated with early or late post-operative adverse events [14–17]. A previous study in Crohn's disease patients reported that

*Abbreviations:* IBD, Inflammatory bowel disease; UC, ulcerative colitis; anti-TNF, anti-tumor necrosis factor; IFX, infliximab; IPAA, ileal pouch-anal anastomosis

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https://doi.org/10.1016/j.ijsu.2019.03.016
Received 23 November 2018; Received in revised form 15 January 2019; Accepted 22 March 2019
Available online 26 March 2019

preoperative exposure to anti-TNF therapy causes a unique histologic pattern of dense, paucicellular hyalinizing fibrosis in the submucosa and a decrease in mucosal and submucosal inflammation [18]. However, in UC patients, it is not clear whether anti-TNF therapy increases histological measures of fibrosis in the colorectum. We hypothesized that dense submucosal fibrosis, if present, may be a factor in adverse anastomosis complications following IPAA surgery in UC patients. As such, we sought to determine whether preoperative exposure to anti-TNF therapy affects histological measures of fibrosis in the colorectal resection specimens of UC patients undergoing IPAA.

## 2. Methods

### 2.1. Study population

This was a single center, retrospective cohort study of patients with UC undergoing IPAA at Mount Sinai Hospital in Toronto, Canada. Mount Sinai Hospital treats a large population of IBD patients, and the Inflammatory Bowel Disease Surgical Database has prospectively collected clinical and demographic data for all IBD patients undergoing surgery at the hospital. Published data from this database has been utilized to evaluate several other IBD-related topics [8,9,14]. In this present study, the data on all individuals with UC who underwent IPAA from January 2002 to June 2013 were reviewed (n = 758). For the remaining UC patients, clinical data regarding preoperative exposure to infliximab (IFX), adalimumab (ADA) and other anti-TNF agents were collected and used to determine patient eligibility for the treatment or the matched control groups of this study. Anti-TNF drug exposure history was verified by review of inpatient and outpatient clinical records. For each patient, we collected the gender, age at diagnosis, date of diagnosis, IBD subtype, body mass index (BMI), albumin at the date of the IPAA creation, anti-TNF exposure, duration of treatment, and the time from the last infusion date to surgery (0–14 days, 15–30 days, 31–180 days and more than 180 days). In addition, we collected the cumulative dosage of anti TNF therapy for each patient. We defined maintenance therapy as accumulate dose > 4 infusion/injection of Anti TNF therapy before first stage surgery. Pouch leaks were documented by clinical and radiologic means. An early leak was defined as occurring from IPAA creation to 1 month of the last surgical procedure, and a late leak was defined as being documented up to 6–12 months after the last surgical stage. We also gathered the following information by reviewing both inpatient and outpatient charts: prednisone ($\geq$15 mg/d) within 30 days from the first stage surgery, intravenous corticosteroids (CS) exposure within 7 days from the first stage surgery, azathioprine or 6-mercaptopurine (6-MP) exposure within 3 months of surgery, date of hospitalization, date of surgery, age at surgery, main operative procedure, surgical technique (open vs. laparoscopic), post-operative complication (infectious and non-infectious), and disease severity and extension as per the Montreal classification [19].

Patients undergoing both three-stage and two-stage IPAA procedures were included. A three-stage procedure involves subtotal colectomy (first stage), IPAA and creation of a defunctioning ileostomy (second stage), and finally closure of the ileostomy (third stage). A two-stage procedure involves either: a) total abdominal proctocolectomy, IPAA, and creation of a defunctioning ileostomy (first stage), followed by closure of the defunctioning ileostomy (second stage); or b) subtotal colectomy and end ileostomy (first stage), followed by IPAA without defunctioning ileostomy (second stage).

This study was approved by the Mount Sinai Hospital Institutional Research Ethics Board. The work was reported in line with the STROCSS criteria [20].

### 2.2. Treatment group

Individuals receiving IFX as maintenance therapy (a priori defined as more than four doses of IFX) with their last dose within 180 days of the first stage of the IPAA procedure were eligible to be included in the treatment group (n = 108). A sample size of 65 treated patients and 65 matched controls was adequate to achieve > 80% statistical power to detect histological fibrosis changes. Therefore, from within the eligible treatment group, a sample of 76 treated patients were randomly selected for inclusion in the study. Eleven patients were excluded because archived pathological slides or sample blocks were not available at our institution. The final treatment group comprised 65 patients. Additional clinical information including indication for surgery, postoperative length of stay, and rates of wound infection and pelvic abscess, was collected for all patients and compared between the treatment and control groups to ensure there were no significant measurable differences in the clinical status between the groups.

### 2.3. Control group

Patients with no history of exposure to anti-TNF at any point in their disease course and who had histological material available for evaluation were eligible for inclusion in the control group (n = 300). From this group, 65 patients were selected for inclusion in the study selected by matching 1:1 with the treatment group based on age, gender, UC disease duration, body mass index (BMI), albumin level at the time of colectomy, and the presence or absence of a postoperative pouch leak within 30 days after surgery.

### 2.4. Primary outcome measure

The primary objective of this study was to determine whether preoperative exposure to anti-TNF therapy affects histological measures of fibrosis in the rectum, as increased rectal fibrosis may be a potential factor in adverse anastomosis complications following IPAA surgery. Therefore, to estimate the extent of rectal fibrosis, the most distal, well-oriented, full-thickness section taken from patients' colectomy specimens were evaluated. This anatomic location would have been immediately adjacent to the small cuff of remaining rectum to which the pouch was ultimately anastomosed, and thus was thought to be most representative of the degree of fibrosis in the residual rectum. In patients undergoing 3-stage procedures, the most distal well-oriented section from the patients' subtotal colectomies were evaluated. The rectal stump was not selected for evaluation because of the potential confounding effects of diversion proctitis.

H&E and Masson's trichrome slides were evaluated. Assessment of the degree of fibrosis in all large bowel layers was performed, including within the lamina propria, the submucosa (SM), the SM immediately above the muscularis propria (MP), and the subserosa. The SM immediately above the MP rather than the MP itself was selected for evaluation based on the early observation that fibrosis was accentuated in this area in some patients, while no MP fibrosis was observed [18]. In our study, a portion of the sample was evaluated by two GI pathologists (JM, RR). There was excellent consistency between the two pathologists, and the remainder of the sample was therefore assessed by one pathologist (JM) blinded to the subjects' preoperative anti-TNF exposure history. The degree of fibrosis was scored on a scale of 1–4, based on a semi-quantitative pictorial scale created for this purpose (Fig. 1). A score of 1 represents minimal to no fibrosis and a score of 4 represents severe fibrosis.

### 2.5. Statistical analysis

Clinical characteristics for matched patients were compared between the treatment and control groups. Frequency (percentage) or median ( ± interquartile range) were reported. Significance was assessed by Pearson Chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables, respectively.

The fibrosis score was treated as a categorical variable. Fibrosis scores for each large bowel layer were compared between matched

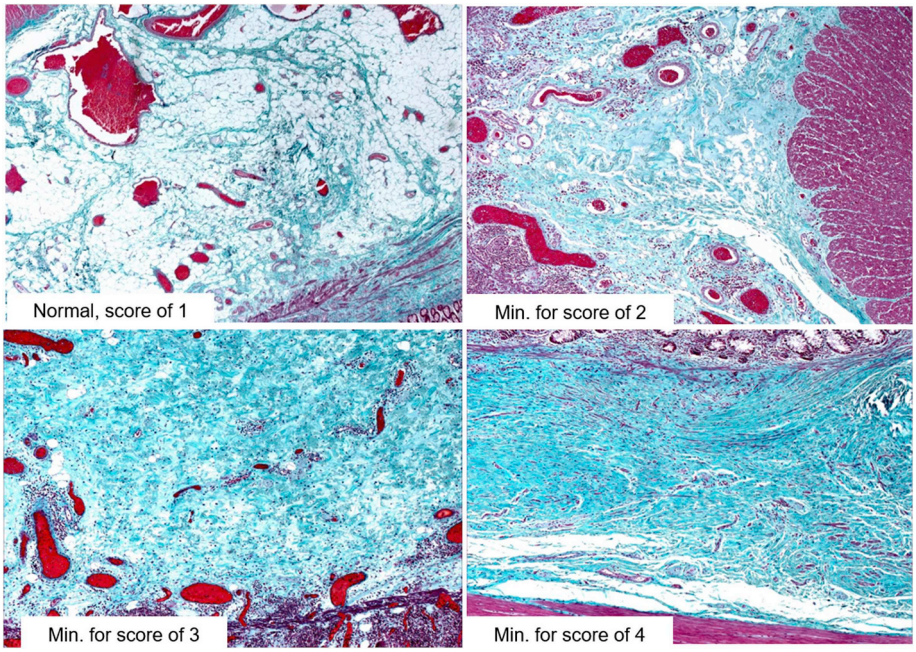


**Fig. 1.** The visual scale used to assign fibrosis scores. Slides cut from formalin-fixed, paraffin-embedded tissue were stained manually with a trichrome stain.

patients in the treatment and control groups using the McNemar-Bowker test. A sample size of 65 treated patients and 65 matched controls was adequate to achieve > 80% statistical power to detect histological fibrosis changes. All analyses were conducted using SAS v.9.2 (SAS Institute Inc., Cary, NC) with $p < 0.05$ considered significant.

## 3. Results

### 3.1. Clinical characteristics of study population

Seven hundred ninety-eight IBD patients who had IPAA procedures between 2002 and 2013 were reviewed. We excluded 25 CD patients and 15 patients with incomplete information. The treatment group comprised 65 patients selected randomly from among the 108 patients who received maintenance anti-TNF therapy within 180 days of the first stage of IPAA surgery. The control group comprised 65 patients who never received anti-TNF therapy, matched 1:1 with patients in the treatment group for age, gender, BMI, UC disease duration, albumin levels, and post-operative leak outcome. There were no significant differences in demographic or clinical variables between the anti-TNF treatment group and the non-exposed group (Table 1). In particular, the rate of infectious complications (presence of wound infection or pelvic abscess) was similar in the anti-TNF exposed group compared to the non-exposed groups (12.3% vs. 7.6%, p = 0.41 for wound infection, 18.4% vs. 23%, p = 0.41 for pelvic abscess, respectively). There were also no significant differences in the postoperative IPAA leak rate between the exposed and control groups (10.7% vs. 13.8%, p = 0.16).

### 3.2. Fibrosis scores

Histological fibrosis in the 65 patients from the therapy group was compared to that in 65 patients from the matched control group. Fibrosis scores for each large bowel layer assessed are presented in Table 2 and Fig. 2. Overall, there was no statistically significant difference in fibrosis scores between the treatment and control groups at any histologic level of the bowel wall. In the lamina propria, 29% of the control group and 28% of the treatment group had fibrosis scores ≥3. Fibrosis scores were higher in the submucosa, with both groups having 66% of patients showing scores ≥3. Similarly, in the region above the muscularis propria, 77% of the control group and 80% of the treatment group had fibrosis scores ≥3. In the subserosa, fibrosis scores were lower, with 25% of the control group and 32% of the treatment group having fibrosis scores ≥3.

**Table 1**
Clinical characteristics of IPAA study population.

| | Control (n = 65) | Anti TNF treated group (n = 65) | p value |
|---|---|---|---|
| Female gender, n (%) | 27 (41.5) | 29 (44.0) | 0.56 |
| Age at surgery (yrs), median (IQR) | 35 (25, 42) | 32 (25, 40) | 0.38 |
| Disease duration (yrs), median (IQR) | 5.8 (2.9, 10.4) | 5.3 (4.0, 9.3) | 0.35 |
| Albumin before STC, median (IQR) | 40.5 (32, 43.5) | 40 (35, 42) | 0.80 |
| Body mass index, median (IQR) | 24.1 (21.1, 26.8) | 23.4 (21.6, 29.1) | 0.10 |
| Postoperative LOS, median (IQR) | 9 (7, 12) | 9 (7, 11) | 0.22 |
| Wound infection, n (%) | 5 (7.6) | 8 (12.3) | 0.41 |
| Pelvic abscess, n (%) | 15 (23.0) | 12 (18.4) | 0.41 |
| Indication for surgery, n (%) | | | |
| Refractory to medication | 57 (87.6) | 58 (89.2) | 0.51 |
| Acute UC/toxic megacolon | 4 (6.1) | 1 (1.5) | |
| Dysplasia/malignancy | 8 (12.3) | 2 (3.0) | |
| Anastomotic leak, n (%) | 9 (13.8) | 7 (10.7) | 0.16 |

LOS: Length of stay, STC: Subtotal colectomy. IPAA: Ileal-pouch anal anastomosis. UC, ulcerative colitis.

**Table 2**
Histological score.

| | Control (n = 65) | Anti TNF Treated Group[a] (n = 65) | p Value |
|---|---|---|---|
| Fibrosis in Lamina propria, n (%) | | | 0.18 |
| 1 | 25 (38.4) | 26 (40.0) | |
| 2 | 21 (32.3) | 21 (32.3) | |
| 3 | 5 (7.7) | 11 (16.9) | |
| 4 | 14 (21.5) | 7 (10.8) | |
| Fibrosis in submucosa, n (%) | | | 0.29 |
| 1 | 8 (12.3) | 6 (9.2) | |
| 2 | 14 (21.5) | 16 (24.6) | |
| 3 | 27 (41.5) | 23 (35.4) | |
| 4 | 16 (24.6) | 20 (30.8) | |
| Fibrosis above muscularis propria (%) | | | 0.36 |
| 1 | 5 (7.6) | 0 (0) | |
| 2 | 10 (15.4) | 13 (20.0) | |
| 3 | 27 (41.5) | 22 (33.8) | |
| 4 | 23 (35.4) | 30 (46.2) | |
| Fibrosis in subserosa, n (%) | | | 0.71 |
| 1 | 26 (40.0) | 22 (33.8) | |
| 2 | 23 (35.4) | 22 (33.8) | |
| 3 | 10 (15.4) | 14 (21.5) | |
| 4 | 6 (9.2) | 7 (10.8) | |

Significance was assessed using the McNemar-Bowker test.

[a] Anti TNF-α Treated Group-defined as patients on Anti TNF-α maintenance therapy, at least 4 4 infusion/doses of anti TNF and within 180 day before the Subtotal colectomy.

## 4. Discussion

We believe this is the first matched, controlled study to evaluate the effects of anti-TNF therapy on the histopathology of resected colorectal specimens from subjects with UC undergoing IPAA. Compared to anti-TNF-naïve matched controls, we found that resection specimens from UC patients treated with maintenance anti-TNF therapy showed no significant differences in the degree of histologic fibrosis in the lamina propria, submucosa, submucosa just above the muscularis propria, or the subserosa. In our previous publication, we showed that maintenance anti-TNF therapy prior to IPAA surgery does not increase the risk of anastomosis failure or IPAA leak due to colonic fibrosis [14].

In contrast to our present results, Schaeffer et al. found significant submucosal fibrosis in resection specimens of subjects with Crohn's disease (CD) who underwent surgery following anti-TNF therapy compared to matched controls who had not received anti-TNF therapy within 180 days prior to surgery [18]. These results seem contrary to expectations, because anti-TNF therapy combats the underlying inflammation that leads to fibrosis [21]. However, as Schaeffer points out, it is possible that anti-TNF therapy causes a disruption in the balance between TNF-α and transforming growth factor-β (TGF-β), which are antagonistic cytokines with respect to their effects on collagen I. TNF-α downregulates collagen I gene expression, while TGF-β has the opposite effect, up regulating collagen I and promoting fibrosis by enhancing extracellular matrix (ECM) deposition [22]. TGF-β has also been shown in multiple studies to be upregulates in active CD and UC [23,24].

Other reports however, call into question the role of anti-TNF therapy in the promotion of fibrosis. A recent large, multicenter study of pediatric CD patients suggested that, in patients who go on to develop strictures later in their disease course, a pro-fibrotic gene signature is detectable in intestinal mucosa at the time of IBD diagnosis, well before the development of strictures [25]. In this cohort, anti-TNF therapy was effective in preventing penetrating complications, but had no effect on the development of strictures. These findings are in keeping with our observation in the current study that histologic fibrosis was independent of treatment with anti-TNF therapy. Moreover, there is also some evidence that colonic fibrosis may ultimately become a self-perpetuating process which can occur even in the absence of inflammation, perhaps suggesting why treatments focused on reducing inflammation do not necessarily prevent strictures. This is thought to occur through the activation of mesenchymal cells via integrins, which are cell surface receptors that transmit signals from the stiff ECM to

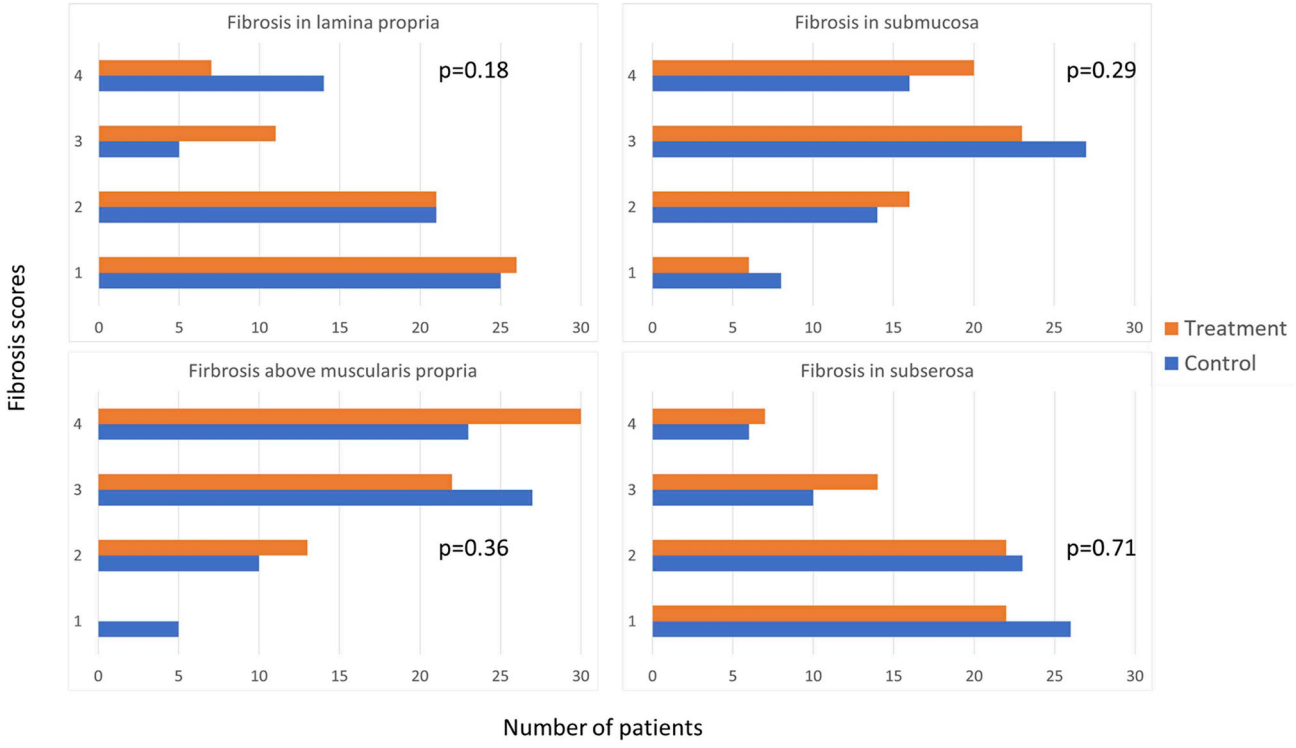


**Fig. 2.** Fibrosis scores in each of the bowel layers assessed. The y-axis represents the fibrosis score (1–4) and the x-axis represents the number of patients achieving that score. The treatment group is shown in orange and the control group is in blue. There were no significant differences in the fibrosis scores between the treatment and control groups for any of the bowel layers. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

fibroblasts [26]. These extracellular signals, in addition to TGF-β signaling, activate a kinase cascade within the mesenchymal cells that includes Rho-associated protein kinase (ROCK), which leads to fibrosis [27]. In fact, ROCK inhibitors are currently being explored as novel anti-fibrotic therapeutic agents [28].

While our study found no statistically significant differences in the degree of fibrosis between the treatment and control groups with respect to anti-TNF therapy prior to IPAA surgery, fibrosis is still a problem for UC patients. The reported prevalence of fibrosis-associated colonic strictures in UC patients is between 1.5% and 11.2% compared to 8% in CD patients [29,30]. In addition, multiple studies have found that 100% of histological specimens collected from UC patients undergoing colectomy had some degree of fibrosis even without stricture, which appears to be proportional to the degree of inflammation [31]. The degree of inflammation is also related to disease duration, which we controlled for in this present study by matching treatment and control groups to UC disease duration.

The gut microbiome has also been implicated as an important profibrotic factor, particularly in UC patients, due to the dense colonic microbiota compared to the sparsely populated small bowel microbiota [25,32]. Ligands like flagellin from both gram-positive and gram-negative bacteria of the gut microbiota are thought to activate toll-like receptors (TLR2, TLR4 and TLR5), which activate the NF-κB cascade resulting in profibrotic cytokine and chemokine secretion by colonic mesenchymal cells that are suspected to contribute to fibrosis [33,34]. Our study supports the notion that fibrosis is driven by mechanisms other than TNF in UC patients.

Our study had several limitations. First, it is acknowledged that the sample size was relatively small. However, importantly, we obtained sufficient statistical power and used matched controls to help minimize confounding. Second, there is potential selection bias, since we were only able to use colectomy specimens from refractory UC patients. Thus, our study population was limited to UC patients who were non-responders to anti-TNF therapy, indicating the inflammatory process was not driven by TNF. It is important to note, however, that this cohort was necessary in order to obtain resection specimens to examine all layers of the large bowel for the presence or absence of fibrosis. The alternative of endoscopic biopsy, which could have included UC patients who were non-refractory and responsive to anti-TNF therapy, can only visualize the mucosal layer of the colon and was therefore insufficient for our study. Third, this is a retrospective study that represents data from a single, large tertiary IBD center in North America. However, One of the strengths of our study is that it included well-matched groups with similar demographic and clinical profiles to minimize confounding variables.

We acknowledge that a prospective, multi-center study in the future would be ideal to better understand the influence of anti-TNF therapy on fibrosis but, such a study would be difficult to perform.

Currently, the decision about performing IPAA in UC patients in two stages or three stages, is largely based on the clinical severity of the disease with consideration regarding the degree of inflammation as well as the preoperative exposure to anti-TNF, immunosuppressants and steroid therapies [35]. In our study we controlled for these major confounders finding that, in contrast to previous reports [35–37], preoperative exposure to anti-TNF in UC patients who underwent IPAA is not associated with increased fibrosis.

## 5. Conclusion

In summary, in a large cohort of UC patients who underwent IPAA surgery at a single, tertiary care center, the resection specimens from UC patients treated with maintenance anti-TNF therapy who underwent IPAA surgery showed no significant differences in the degree of histologic fibrosis compared to a matched control group. Based on our findings, exposure to anti-TNF therapy in UC patients should not play a significant role in surgical decision-making regarding possible adverse anastomosis complications due to fibrosis in the colorectum following IPAA surgery.

## Ethical approval

This study was approved by the Mount Sinai Hospital Institutional Research Ethics Board.

## Sources of funding

None.

## Author contribution

EZ, JM, ZC, IMG, RR and MSS - Study concept and design; acquisition of data; analysis & data interpretation; critical revision of the manuscript for important intellectual content.

EZ, JM, MB – Writing of the manuscript.

RM - Data collection, critical revision of the manuscript for important intellectual content.

## Conflicts of interest

EZ-has received research support and consulting fees from Janssen, Abbvie, Takeda, Neopharm, Pfizer.

JM-None.

RM-None.

MB-None.

ZC-None.

IMG - None.

RR-None.

MSS - received research support and consulting fees from Janssen, Abbvie, Takeda, and Prometheus.

## Research registration unique identifying number (UIN)

NCT03747068.

## Guarantor

EZ, JM, RR and MSS – accept full responsibility for the conduct of the study.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Data statement

Due to the confidential patient's details in this study, survey respondents were assured raw data would remain confidential and would not be shared.

## Acknowledgments

The authors would like to thank Huang Harden, Salah Metwaly and Brenda O'Connor for assistance in managing the data from the IBD surgical database; Joanne Stempak for assistance with the REB approval.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.03.016.

## References


[1] E. Langholz, P. Munkholm, M. Davidsen, V. Binder, Course of ulcerative colitis: analysis of changes in disease activity over years, Gastroenterology 107 (1994) 3–11.

[2] J. Allison, L.J. Herrinton, L. Liu, J. Yu, J. Lowder, Natural history of severe ulcerative colitis in a community-based health plan, Clinical gastroenterology and hepatology: the official clinical practice, J. Am. Gastroenterol. Assoc. 6 (2008) 999–1003.

[3] M.J. Etchevers, M. Aceituno, O. Garcia-Bosch, I. Ordas, M. Sans, E. Ricart, J. Panes, Risk factors and characteristics of extent progression in ulcerative colitis, Inflamm. Bowel Dis. 15 (2009) 1320–1325.

[4] R.G. Farmer, K.A. Easley, G.B. Rankin, Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients, Dig. Dis. Sci. 38 (1993) 1137–1146.

[5] Z. Cohen, R.S. McLeod, H. Stern, D. Grant, S. Nordgren, The pelvic pouch and ileoanal anastomosis procedure. Surgical technique and initial results, Am. J. Surg. 150 (1985) 601–607.

[6] P.W. Marcello, P.L. Roberts, D.J. Schoetz Jr., J.A. Coller, J.J. Murray, M.C. Veidenheimer, Long-term results of the ileoanal pouch procedure, Arch. Surg. 128 (1993) 500–503 discussion 503-504.

[7] V.W. Fazio, R.P. Kiran, F.H. Remzi, J.C. Coffey, H.M. Heneghan, H.T. Kirat, E. Manilich, B. Shen, S.T. Martin, Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients, Ann. Surg. 257 (2013) 679–685.

[8] E. Zittan, G.W. Ma, N. Wong-Chong, R. Milgrom, R.S. McLeod, M. Silverberg, Z. Cohen, Ileal pouch-anal anastomosis for ulcerative colitis: a Canadian institution's experience, Int. J. Colorectal Dis. 32 (2) (2017 Feb) 281–285.

[9] E. Zittan, N. Wong-Chong, G.W. Ma, R.S. McLeod, M.S. Silverberg, Z. Cohen, Modified two-stage ileal pouch-anal anastomosis results in lower rate of anastomotic leak compared with traditional two-stage surgery for ulcerative colitis, J. Crohn's Colitis 10 (2016) 766–772.

[10] W.J. Sandborn, P. Rutgeerts, B.G. Feagan, W. Reinisch, A. Olson, J. Johanns, J. Lu, K. Horgan, D. Rachmilewitz, S.B. Hanauer, G.R. Lichtenstein, W.J. de Villiers, D. Present, B.E. Sands, J.F. Colombel, Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab, Gastroenterology 137 (2009) 1250–1260 quiz 1520.

[11] P. Rutgeerts, W.J. Sandborn, B.G. Feagan, W. Reinisch, A. Olson, J. Johanns, S. Travers, D. Rachmilewitz, S.B. Hanauer, G.R. Lichtenstein, W.J. de Villiers, D. Present, B.E. Sands, J.F. Colombel, Infliximab for induction and maintenance therapy for ulcerative colitis, N. Engl. J. Med. 353 (2005) 2462–2476.

[12] C. Rungoe, E. Langholz, M. Andersson, S. Basit, N.M. Nielsen, J. Wohlfahrt, T. Jess, Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011, Gut 63 (2014) 1607–1616.

[13] F. Selvaggi, G. Pellino, S. Canonico, G. Sciaudone, Effect of preoperative biologic drugs on complications and function after restorative proctocolectomy with primary ileal pouch formation: systematic review and meta-analysis, Inflamm. Bowel Dis. 21 (2015) 79–92.

[14] E. Zittan, R. Milgrom, G.W. Ma, N. Wong-Chong, B. O'Connor, R.S. McLeod, H.M. MacRae, G.R. Greenberg, G.C. Nguyen, K. Croitoru, A.H. Steinhart, Z. Cohen, M.S. Silverberg, Preoperative anti-tumor necrosis factor therapy in patients with ulcerative colitis is not associated with an increased risk of infectious and non-infectious complications after ileal pouch-anal anastomosis, Inflamm. Bowel Dis. 22 (2016) 2442–2447.

[15] M. Ferrante, A. D'Hoore, S. Vermeire, S. Declerck, M. Noman, G. Van Assche, I. Hoffman, P. Rutgeerts, F. Penninckx, Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis, Inflamm. Bowel Dis. 15 (2009) 1062–1070.

[16] G. Rizzo, A. Armuzzi, D. Pugliese, A. Verbo, A. Papa, C. Mattana, G.L. Rapaccini, L. Guidi, C. Coco, Anti-TNF-alpha therapies do not increase early postoperative complications in patients with inflammatory bowel disease. An Italian single-center experience, Int. J. Colorectal Dis. 26 (2011) 1435–1444.

[17] C.W. Hicks, R.A. Hodin, L. Bordeianou, Possible overuse of 3-stage procedures for active ulcerative colitis, JAMA surgery 148 (2013) 658–664.

[18] D.F. Schaeffer, J.C. Walsh, R. Kirsch, M. Waterman, M.S. Silverberg, R.H. Riddell, Distinctive histopathologic phenotype in resection specimens from patients with Crohn's disease receiving anti-TNF-alpha therapy, Hum. Pathol. 45 (2014) 1928–1935.

[19] J. Satsangi, M.S. Silverberg, S. Vermeire, J.F. Colombel, The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications, Gut 55 (2006) 749–753.

[20] R.A. Agha, M.R. Borrelli, M. Vella-Baldacchino, R. Thavayogan, D.P. Orgill, S. Group, The STROCSS statement: strengthening the reporting of cohort studies in surgery, Int. J. Surg. 46 (2017) 198–202.

[21] I. Ordas, B.G. Feagan, W.J. Sandborn, Early use of immunosuppressives or TNF antagonists for the treatment of Crohn's disease: time for a change, Gut 60 (2011) 1754–1763.

[22] F. Verrecchia, A. Mauviel, TGF-beta and TNF-alpha: antagonistic cytokines controlling type I collagen gene expression, Cell. Signal. 16 (2004) 873–880.

[23] J.P. Burke, M. Ferrante, K. Dejaegher, R.W. Watson, N.G. Docherty, G. De Hertogh, S. Vermeire, P. Rutgeerts, A. D'Hoore, F. Penninckx, K. Geboes, G. Van Assche, P.R. O'Connell, Transcriptomic analysis of intestinal fibrosis-associated gene expression in response to medical therapy in Crohn's disease, Inflamm. Bowel Dis. 14 (2008) 1197–1204.

[24] M.W. Babyatsky, G. Rossiter, D.K. Podolsky, Expression of transforming growth factors alpha and beta in colonic mucosa in inflammatory bowel disease, Gastroenterology 110 (1996) 975–984.

[25] S. Kugathasan, L.A. Denson, T.D. Walters, M.O. Kim, U.M. Marigorta, M. Schirmer, K. Mondal, C. Liu, A. Griffiths, J.D. Noe, W.V. Crandall, S. Snapper, S. Rabizadeh, J.R. Rosh, J.M. Shapiro, S. Guthery, D.R. Mack, R. Kellermayer, M.D. Kappelman, S. Steiner, D.E. Moulton, D. Keljo, S. Cohen, M. Oliva-Hemker, M.B. Heyman, A.R. Otley, S.S. Baker, J.S. Evans, B.S. Kirschner, A.S. Patel, D. Ziring, B.C. Trapnell, F.A. Sylvester, M.C. Stephens, R.N. Baldassano, J.F. Markowitz, J. Cho, R.J. Xavier, C. Huttenhower, B.J. Aronow, G. Gibson, J.S. Hyams, M.C. Dubinsky, Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study, Lancet 389 (2017) 1710–1718.

[26] L.A. Johnson, E.S. Rodansky, K.L. Sauder, J.C. Horowitz, J.D. Mih, D.J. Tschumperlin, P.D. Higgins, Matrix stiffness corresponding to strictured bowel induces a fibrogenic response in human colonic fibroblasts, Inflamm. Bowel Dis. 19 (2013) 891–903.

[27] L.A. Johnson, E.S. Rodansky, A.J. Haak, S.D. Larsen, R.R. Neubig, P.D. Higgins, Novel Rho/MRTF/SRF inhibitors block matrix-stiffness and TGF-beta-induced fibrogenesis in human colonic myofibroblasts, Inflamm. Bowel Dis. 20 (2014) 154–165.

[28] F. Rieder, ROCKing the field of intestinal fibrosis or between a ROCK and a hard place? Gastroenterology 153 (2017) 895–897.

[29] J.R. de Bruyn, S.L. Meijer, M.E. Wildenberg, W.A. Bemelman, G.R. van den Brink, G.R. D'Haens, Development of fibrosis in acute and longstanding ulcerative colitis, J. Crohn's Colitis 9 (2015) 966–972.

[30] H.I. Goldberg, S.B. Caruthers Jr., J.A. Nelson, J.W. Singleton, Radiographic findings of the national cooperative Crohn's disease study, Gastroenterology 77 (1979) 925–937.

[31] F. Rieder, C. Fiocchi, G. Rogler, Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases, Gastroenterology 152 (2017) 340–350 e346.

[32] I.O. Gordon, N. Agrawal, J.R. Goldblum, C. Fiocchi, F. Rieder, Fibrosis in ulcerative colitis: mechanisms, features, and consequences of a neglected problem, Inflamm. Bowel Dis. 20 (2014) 2198–2206.

[33] J.M. Otte, I.M. Rosenberg, D.K. Podolsky, Intestinal myofibroblasts in innate immune responses of the intestine, Gastroenterology 124 (2003) 1866–1878.

[34] F. Rieder, The gut microbiome in intestinal fibrosis: environmental protector or provocateur? Sci. Transl. Med. 5 (2013) 190ps110.

[35] I.J. Mor, J.D. Vogel, A. da Luz Moreira, B. Shen, J. Hammel, F.H. Remzi, Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy, Dis. Colon Rectum 51 (2008) 1202–1207 discussion 1207-1210.

[36] S.D. Holubar, R.R. Cima, J.H. Pemberton, Does infliximab increase complications after surgery for inflammatory bowel disease? F1000 medicine reports (2009) 1.

[37] C.R. Selvasekar, R.R. Cima, D.W. Larson, E.J. Dozois, J.R. Harrington, W.S. Harmsen, E.V. Loftus Jr., W.J. Sandborn, B.G. Wolff, J.H. Pemberton, Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis, J. Am. Coll. Surg. 204 (2007) 956–962 discussion 962-953.