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Preoperative infliximab treatment and postoperative complications after laparoscopic restorative proctocolectomy with ileal pouch–anal anastomosis: a case-matched study

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Abstract
Background Infliximab offers promising new therapeutic options for treatment of moderate to severe ulcerative colitis. However, several studies suggest that it increases postoperative complication rates for patients who later require a restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA). This study aimed to assess the postoperative course of patients after laparoscopic IPAA, comparing those who had and those who had not received infliximab before surgery.
Methods The authors identified patients from their institution's IPAA database, finding 13 patients who had received preoperative infliximab treatment. Using age, gender, and type of procedure (2 or 3 stages) as criteria, they matched these cases with infliximab-naive patients drawn from the same database. The differences in perioperative data between the two groups were analyzed. Complications and their severity were assessed using the Strasberg classification.
Results No significant difference was found between patients treated with and those treated without infliximab for each variable studied, namely, mean operative time (353 vs. 355 min), complication rate (23 vs. 38%), and mean hospital stay (22 vs. 25 days).
Conclusion The study findings showed no adverse impact from previous infliximab therapy on the laparoscopic IPAA postoperative course.

Keywords Complications · Ileal pouch anal anastomosis · Infliximab · Laparoscopy · Ulcerative colitis

Infliximab (IFX) has recently become an option for the medical management of ulcerative colitis (UC) in both induction [1–3] and maintenance [4] therapy for moderate to severe ulcerative colitis. Although work has demonstrated the efficacy of IFX including a reduced need for emergency colectomy in severe ulcerative colitis, the rates for delayed colectomy remain high [5]. Moreover, little is known about the impact of IFX on the surgical plan and the surgical complication rates. It seems that IFX does not increase postoperative complications after abdominal surgery for Crohn's disease [6, 7]. However, several reports suggest that preoperative treatment with IFX adversely affects outcomes after surgery for ulcerative colitis [8, 9]. Because other studies contradict these data, a debate now surrounds this issue [10–12].

Restorative proctocolectomy (RPC) with ileal pouch–anal anastomosis (IPAA) has become the procedure of choice for the majority of patients with ulcerative colitis [13]. It allows complete removal of the disease-affected mucosa, with acceptable functional results. The decision whether to perform a one-, two-, or three-stage procedure rests with the surgeon and depends mainly on systemic illness severity and the degree of inflammation.

A recent metaanalysis confirmed the feasibility and safety of laparoscopic IPAA [14]. However, published studies on IFX-related postoperative complications have not yet addressed features specific to laparoscopy. Our

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study aimed to assess the effects of preoperative IFX therapy on postlaparoscopic IPAA morbidity.

Methods

Surgical technique

We previously described our surgical technique [15]. Briefly, we use five or six laparoscopic ports to mobilize the colon, ligate vascular structures, and dissect the rectum to the level of the pelvic floor. A 5- to 7-cm incision at the chosen stoma site permits removal of the specimen and construction of the J-pouch. We perform the double-stapled IPAA laparoscopically. All patients receive a covering ileostomy, with closure occurring at least 8 weeks after the IPAA. Healing of the IPAA is systematically verified by an opaque enema. This corresponds to the two-stage RPC with IPAA.

When a three-stage procedure is performed, the first stage is a subtotal colectomy with an end-ileostomy and sigmoidostomy. The second stage completes the proctocolectomy and constructs the IPAA with a diverting ileostomy. Ileostomy reversal is the third stage.

Patient selection

We reviewed the medical notes for patients who had undergone a laparoscopic IPAA, retrieving them from records kept in a database at our institution since 1999. This database includes medical and surgical history, operation report summaries (operative time, technical difficulties, and conversion to laparotomy), delays in ileostomy reversal, immediate postoperative course, and surgical and functional follow-up assessments.

From this database, we identified patients who had been treated preoperatively with infliximab (Rémicade) for refractory ulcerative colitis. We then matched these patients with IFX-naïve patients on the basis of gender, age, and procedure type (2 or 3 stages).

Outcome measurements

We examined the medical records for age, gender, comorbidity, body mass index (BMI), delay between the initial ulcerative colitis diagnosis and the date of surgery, and number of preoperative IFX doses. We also recorded the procedure type and duration as well as any delays before ileostomy reversal. The total hospital length of stay was the sum of every hospitalization period for each stage of the procedure. In addition, we calculated this variable by including rehospitalizations for complications arising during the outpatient period.

Our study defined indications for surgery as treatment failure for cases showing no improvement after medical treatment and treatment resistance for cases in which patients relapsed at medication weaning after an initial improvement. We noted every complication occurring within 30 days of the ileostomy reversal and graded them according to the Strasberg classification of surgical complications [16].

Statistical analysis

Group matching was assessed with the Mann–Whitney *U* test. Indications for surgery were analyzed using Pearson's chi-square test. We compared the complication rate between the two groups for each Strasberg grade using Pearson's test. The global complication rate (of any Strasberg grade) was evaluated using Fisher's exact test. Age, BMI, delay between initial diagnosis and surgery, procedure duration, and hospital stay including and excluding rehospitalizations and delays before ileostomy reversal were tested using the Mann–Whitney *U* test. A p value of 0.05 or less was considered to be statistically significant.

Results

From May 1999 to December 2008, we performed 75 laparoscopic RPCs with IPAA. Our database identified 13 patients treated preoperatively with IFX who ultimately underwent an RPC with IPAA (IFX group). Each of these 13 patients received their last IFX dose within a median period of 44 days (range, 13–167 days) before surgery. We matched these 13 patients with 13 IFX-naive patients who underwent the same procedure (non-IFX group).

Table 1 summarizes the sample characteristics. The two groups were well-matched for age, and no statistically significant difference was found for BMI, delay between initial diagnosis and surgery, or indications for surgery between the two groups.

Table 2 summarizes perioperative data. No significant difference was found in mean operative time between the two groups. The operation notes mentioned no perioperative complications, and the conversion rate was zero.

For postoperative complication rates as well, no significant difference was found between the two groups. In the IFX group, three postoperative complications occurred (23%). One patient required repeat laparoscopy on postoperative day 2 for increased abdominal pain and tenderness, with a pneumoperitoneum diagnosed on computed tomography. However, we discovered no abnormality at laparoscopy, and subsequent recovery was uneventful. One patient experienced a pelvic abscess, which responded to antibiotics alone.

In the non-IFX group, five postoperative complications occurred (38%). One patient experienced a small bowel

Table 1 Characteristics of patients treated (IFX) and not treated (non-IFX) with infliximab (IFX)

	IFX	Non-IFX	*p* Value
Patients (*n*)	13	13	–
Two-stage procedure (*n*)	7	7	–
Gender (*n*)			
M	7	7	–
F	6	6	–
Mean no. of preoperative IFX infusions	5 ± 3.5	–	–
Median delay between last IFX infusion and surgery: days (range)	44 (13–167)	–	–
Mean age (years)	32.8 ± 12.6	34.1 ± 13.9	0.810
Mean BMI	21.9 ± 2.2	20.2 ± 2.6	0.180
Comorbidities: *n* (%)			
Ischemic cardiomyopathy	1 (8)	1 (8)	–
Sclerosing cholangitis	0	1 (8)	–
Autoimmune pancreatitis	2 (15)	0	–
Mean delay between initial UC diagnosis and surgery (years)	5.4 ± 4.3	8.7 ± 9.9	0.900
Indications (*n*)	8	7	
Treatment failure/treatment resistance	5	6	0.691
Supplemental preoperative treatments: *n* (%)			
Corticosteroids	6 (46)	5 (38)	–
Cyclosporine A	2 (15)	7 (54)	–
Azathioprine	7 (54)	1 (8)	–

BMI body mass index, *UC* ulcerative colitis

Table 2 Comparison of perioperative ileal pouch–anal anastomosis (IPAA) features between patients treated (IFX) and not treated (non-IFX) with infliximab (IFX)

	IFX	Non-IFX	*p* Value
Mean duration of RPC with IPAA (min)[a]	386.4 ± 83.8	395.7 ± 66.8	0.90
Mean duration of proctectomy completion with IPAA (min)[b]	314.1 ± 53	306.7 ± 80.1	0.42
Intraoperative complications (*n*)	0	0	–
Conversion to open procedure (*n*)	0	0	–
Postoperative complications (*n*)	3	5	0.41
Small bowel obstruction	1	1	
Pelvic abscess	1	0	
Postoperative pneumoperitoneum	1	0	
Anastomotic leak	0	1	
Pleural effusion	0	1	
Anastomotic hemorrhage	0	1	
Small bowel perforation	0	1	
Clavien (*n*)			
1	1	1	0.68
2	1	1	
3a	0	1	
3b	1	2	
4a	0	0	
4b	0	0	
5	0	0	
Total hospital stay (days)	21.9 ± 0.1	23.9 ± 9.1	0.80
Total hospital stay, including repeat admissions (days)	22.1 ± 6.3	24.9 ± 8.8	0.51
Delay between IPAA and ileostomy reversal (weeks)	11.5 ± 3.2	13.2 ± 12.0	0.63

RPC restorative proctocolectomy

[a] First stage of two-stage RPC with IPAA

[b] Second stage of three-stage RPC with IPAA

obstruction, which we treated with a nothing-by-mouth regimen and a nasogastric tube until flatus resumed. Accidental small bowel perforation occurred during the original procedure for one patient, which was diagnosed at laparoscopy on postoperative day 1.

The two groups did not differ significantly in the cumulative length of hospital stay, even when additional hospital stays for outpatient complications were taken into account. Delays in ileostomy reversal were not significantly different between the two groups.

Discussion

For patients undergoing a laparoscopic RPC with IPAA for ulcerative colitis, we found no evidence of harmful effects from prior IFX use. Ulcerative colitis is a chronic inflammatory bowel disease that may result from an exaggerated immune response to specific bacterial antigens [17].

High-dose intravenous steroid therapy forms the basis of pharmacologic treatment for acute ulcerative colitis. However, alternative immunosuppressive medications can be used if the exacerbation fails to respond to steroids or if steroid weaning becomes impossible because of relapse. Second-line therapy usually consists of cyclosporine A, with a switch to azathioprine for maintenance therapy.

Since 2001, IFX also has been used as induction therapy for steroid-refractory moderate to severe ulcerative colitis [18], but it also can be used as maintenance therapy [2–4, 19]. Infliximab is a chimeric murine monoclonal antibody that binds to tumor necrosis factor-alpha (TNF-α), a key proinflammatory cytokine implicated in immune mechanisms and wound healing. The colonic mucosa of ulcerative colitis and Crohn's disease, among disorders in other locations, expresses raised levels of TNF-α [20, 21].

However, concerns have developed regarding IFX's potential to affect postoperative complications adversely. The data in Table 3 summarize the studies that assessed complication rates after IPAA for patients treated with IFX for ulcerative colitis. Several studies have reported an increase in postsurgical morbidity after IFX treatment [8, 9], whereas other reports [10–12] contradict these findings. The principal complications studied include pelvic infections and anastomotic leaks, although the reports also cover extraabdominal sepsis (e.g., lung infections) and small bowel obstruction. These studies have heterogeneous designs, and none of them assess complication severity in a reproducible manner. Furthermore, none of them focus on features specific to laparoscopic techniques. Thus, the question of whether IFX influences the postoperative course of laparoscopic IPAA or not remained unanswered.

Studies showing that IFX increases surgical morbidity hypothesize that its biologic effects render patients susceptible to infection. Indeed, inhibiting TNF-α alters immunologic [22, 23] and wound-healing [24, 25] capabilities. Moreover, the safest delay between the last IFX infusion and surgery remains to be assessed. As shown by Mor et al. [8], effects of IFX could be observed even in a comparison of

Table 3 Summary of reports from studies of infliximab (IFX) treatment and postoperative complications after ileal pouch–anal anastomosis (IPAA) for ulcerative colitis (UC)

Study	Study design	UC patients (IFX/non-IFX) (*n*)	IPAA (IFX/non-IFX) (*n*)	Complications studied	Complication rate (IFX/non-IFX) (%)	*p* Value
Ferrante et al. [12]	Retrospective cohort	22/119	9/91	Infection Early	11/29	0.438
Kunitake et al. [10][a]	Retrospective cohort	26/100	NA	All Early	NA	NA
Mor et al. [8]	Retrospective cohort Case-matched study	44/46[b]	46/46	All Early/late	35/15	0.027
Schluender et al. [11]	Retrospective cohort	17/134	17/134	All Early	Medical: 6/10 Surgical: 30/18 Overall infections: 18/8	0.99 0.3 0.2
Selvasekar et al. [9]	Retrospective cohort Multivariate analysis	47/254	47/254	Infection Early	28/10	OR = 2.1 (95% CI = 1.1–4.3)
Current series 2009	Retrospective Case-matched study	13/13	13/13[c]	All Early	23/38	0.41

NA not applicable, data not displayed; *OR* odds ratio; *CI* confidence interval

[a] Study of IFX in all types of inflammatory bowel disease

[b] Two patients were treated for colitis of unknown origin

[c] Exclusively laparoscopic procedures

patients who had their last IFX dosing more than 16 weeks before surgery. They hypothesized that because TNF-α is a part of a complex proinflammatory cascade, not yet completely understood, IFX might alter this mechanism long after it is discharged by the patient's body.

In our series, we could not find a statistically significant difference in the complication rates between the IFX and non-IFX groups. The Strasberg classification of surgical complications [16] allows a standardized and exhaustive comparison of the effects of IFX on the postoperative course. It classifies complications according to their severity and their effects on medical management. Even after correction according to the Strasberg classification, we could not find any statistically significant differences between the two groups. One pelvic abscess occurred in the IFX group of our series, but there was no anastomotic leak to explain this. However, one fistula and one anastomotic hemorrhage occurred in the non-IFX group.

A longer hospital stay can reflect a more difficult postoperative course, even in the absence of obvious complications from causes such as a delayed return of bowel movements or a longer period of bed rest. In our study, the mean length of hospital stay was not different between the two groups, even when rehospitalization periods for outpatient complications were included.

At our institution, ileostomy is closed only when the clinical status permits and radiology shows complete IPAA healing. Thus, the delay between IPAA construction and ileostomy reversal also can reflect postoperative complication rates. We could not find a statistically significant difference between the two groups for this variable. Nor was the laparoscopic IPAA more complex in the IFX group because mean operative time was not significantly different. No intraoperative complications were reported. However, one accidental small bowel perforation occurred in the non-IFX group, although this was diagnosed only on postoperative day 1.

Evidence suggests that IFX improves nutritional status for patients with Crohn's disease, increasing their BMI [26], although whether this also occurs in ulcerative colitis patients is unknown. In our study, although no difference reached statistical significance, every measured variable favored the IFX group. We could hypothesize, therefore, that IFX actually may improve the IPAA postoperative course.

Conclusion

The study findings show a significant difference in the postoperative complication rate between the patients who received preoperative IFX and those who did not. Furthermore, the laparoscopic RPC with IPAA was not more difficult to perform for IFX-treated patients. Whether beneficial or detrimental, the effects of IFX should be studied with a larger sample.

Disclosures Benjamin Coquet-Reinier, Stéphane V. Berdah, Jean-Charles Grimaud, David Birnbaum, Pierre-Alain Cougard, Marc Barthet, Ariadne Desjeux Vincent Moutardier, and Christian Brunet have no conflicts of interest or financial ties to disclose.

References

1. Chey WY (2001) Infliximab for patients with refractory ulcerative colitis. Inflamm Bowel Dis 7(Suppl 1):S30–S33
2. Kohn A, Prantera C, Pera A, Cosintino R, Sostegni R, Daperno M (2002) Anti-tumour necrosis factor alpha (infliximab) in the treatment of severe ulcerative colitis: result of an open study on 13 patients. Dig Liver Dis 34:626–630
3. Su C, Salzberg BA, Lewis JD, Deren JJ, Kornbluth A, Katzka DA, Stein RB, Adler DR, Lichtenstein GR (2002) Efficacy of anti-tumor necrosis factor therapy in patients with ulcerative colitis. Am J Gastroenterol 97:2577–2584
4. Rutgeerts P, Sandborn WJ, Feagan BG (2005) Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 353:2462–2476
5. Aratari A, Papi C, Clemente V, Moretti A, Luchetti R, Koch M, Capurso L, Caprilli R (2008) Colectomy rate in acute severe ulcerative colitis in the infliximab era. Dig Liver Dis 40:821–826
6. Colombel JF, Loftus EV Jr, Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, Harmsen WS, Schleck CD, Sandborn WJ (2004) Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol 99:878–883
7. Gaertner WB, Decanini A, Mellgren A, Lowry AC, Goldberg SM, Madoff RD, Spencer MP (2007) Does infliximab infusion impact results of operative treatment for Crohn's perianal fistulas? Dis Colon Rectum 50:1754–1760
8. Mor IJ, Vogel JD, da Luz Moreira A, Shen B, Hammel J, Remzi FH (2008) Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. Dis Colon Rectum 51:1202–1297; discussion 1207–1210
9. Selvasekar CR, Cima RR, Larson DW, Dozois EJ, Harrington JR, Harmsen WS, Loftus EV Jr, Sandborn WJ, Wolff BG, Pemberton JH (2007) Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. J Am Coll Surg 204:956–962; discussion 962–963
10. Kunitake H, Hodin R, Shellito PC, Sands BE, Korzenik J, Bordeianou L (2008) Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative complications. J Gastrointest Surg 12:1730–1736
11. Schluender SJ, Ippoliti A, Dubinsky M, Vasiliauskas EA, Papadakis KA, Mei L, Targan SR, Fleshner PR (2007) Does infliximab influence surgical morbidity of ileal pouch-anal anastomosis in patients with ulcerative colitis. Dis Colon Rectum 50:1747–1753
12. Ferrante M, D'Hoore A, Vermeire S, Declerck S, Noman M, Van Assche G, Hoffman I, Rutgeerts P, Penninckx F (2009) Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. Inflamm Bowel Dis 15:1062–1070
13. Fazio VW, Ziv Y, Church JM (1995) Ileal pouch–anal anastomosis complications and function in 1005 patients. Ann Surg 222:120–127

14. Ahmed Ali U, Keus F, Heikens JT, Bemelman WA, Berdah SV, Gooszen HG, van Laarhoven CJ (2009) Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. Cochrane Database Syst Rev. doi:10.1002/14651858
15. Berdah SV, Barthet M, Emungania O, Orsoni P, Alliot P, Grimaud JC, Brunet C (2004) Coloproctectomie totale avec anastomose iléoanale en deux temps vidéoassistée. Expérience initiale de 12 cas. Ann Chir 129:332–336
16. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg 240: 205–213
17. Shih DQ, Targan SR (2008) Immunopathogenesis of inflammatory bowel disease. World J Gastroenterol 14:390–400
18. Chey WY, Hussain A, Ryan C, Potter GD, Shah A (2001) Infliximab for refractory ulcerative colitis. Am J Gastroenterol 96:2373–2381
19. Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C, Vilien M, Strom M, Danielsson A, Verbaan H, Hellstrom PM, Magnuson A, Curman B (2005) Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 128: 1805–1811
20. Murch SH, Braegger CP, Walker-Smith JA, MacDonald TT (1993) Location of tumor necrosis factor alpha by immunochemistry in chronic inflammatory bowel disease. Gut 34: 1705–1709
21. Reinecker HC, Steffen M, Witthoett T (1993) Enhanced secretion of tumor necrosis factor-alpha, IL-6, and IL-1-beta by isolated lamina propria mononuclear cells from patients with ulcerative colitis and Crohn's disease. Clin Exp Immunol 94:174–181
22. Scallon BJ, Moore MA, Trinth H (1995) Chimeric anti-TNF-alpha monoclonal antibody CA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. Cytokine 7:251–259
23. Schmidt M, Luegering N, Luegering A (2000) Infliximab exerts antiinflammatory capacity in IBD by induction of apoptosis in monocytes. Gastroenterology 118:3630
24. Albina J, Mastrofrancesco B, Vessella J (2001) HIF-1 expression in healing wounds: HIF-1alpha induction in primary inflammatory cells by TNF-alpha. Am J Physiol Cell Physiol 281:C1971–C1977
25. Lee L, Efron D, Tantry U (2000) Inhibition of tumor necrosis factor-alpha attenuates wound breaking strength in rats. Wound Rep Reg 8:547–553
26. Wiese D, Lashner B, Seidner D (2008) Measurement of nutrition status in Crohn's disease patients receiving infliximab therapy. Nutr Clin Pract 23:551–556