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Previous infliximab therapy and postoperative complications after proctocolectomy with ileum pouch anal anastomosis☆,☆☆,★

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Abstract

Background and aims: It is unclear whether infliximab treatment induces increased complication rates after surgery for ulcerative colitis. Aim was to compare complication rates after pouch surgery in refractory ulcerative colitis patients with versus without previous infliximab therapy.
Methods: We performed a retrospective study evaluating all patients who underwent an ileoanal J-pouch for refractory ulcerative colitis over a four-year period. Postoperative complications, infliximab use and time between last infliximab administration and restorative surgery were assessed. 1-stage procedures (proctocolectomy with pouch, with or without temporary diversion) and 2-stage procedures (emergency colectomy and subsequent completion proctectomy with pouch, with or without temporary diversion) were analyzed separately.
Results: Seventy-two patients were included; 33 underwent 1-stage procedure and 39 had 2-stage surgery. In the 1-stage group, 21 patients (64%) had previous infliximab therapy (median time between last infusion and surgery: 7.1 months (IQR 2.6-8.3)). Infliximab-treated patients had higher incidence of pelvic sepsis (5/21 vs. 0/12; risk difference 24%; 95% CI: 6 to 42, p=0.067) and non-infectious complications (8/21 vs. 1/12; risk difference 30%; 95% CI: 4 to 56, p=0.065). In the 2-stage group, 17 (44%) had previous infliximab therapy (median time between last infusion and surgery: 11.8 months (IQR 7.3-15.5)). Total, infectious, non-infectious

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complication rates and pelvic sepsis rates were similar for infliximab and non-infliximab patients in the 2-stage group.
Conclusions: This small study suggests that infliximab use prior to 1-stage restorative proctocolectomy in patients with UC is associated with increased incidence of pelvic sepsis. A 2-stage procedure in these patients should be considered.

1. Introduction

Steroid dependent ulcerative colitis (UC) can medically be treated with infliximab (IFX), a monoclonal antibody directed against the inflammatory cytokine TNF-alpha.[1] Since the approval of this drug in 2006, this therapy has often been applied as rescue therapy in order to prevent the need for surgery. When surgery is eventually indicated, it is not clear from the literature whether previous IFX treatment increases the risk of postoperative complications.[2–5]

UC that is refractory to all medical therapies should be treated surgically by means of a proctocolectomy with ileal pouch anal anastomosis (IPAA).[6] This procedure can be performed by a 1-stage procedure, being a proctocolectomy with IPAA, or a 2-stage procedure, in which an emergency colectomy is performed in the acute setting followed by a completion proctectomy with IPAA later on.[7] Both approaches can be performed with or without temporary ileal diversion.

Direct postoperative complications such as pelvic sepsis due to anastomotic leakage or a presacral abscess are known to increase the risk of pouch failure. This will significantly impair long-term quality of life.[8] It is therefore of utmost importance to minimize the incidence of pelvic sepsis after pouch surgery.

If IFX therapy that has been given within months before restorative surgery is associated with higher morbidity jeopardizing long-term pouch function, a 2-stage procedure can be chosen to increase the interval between IFX administration and restorative surgery. In that case, extending the period between last administration of IFX therapy and pouch surgery might lower the complication risk. Therefore, the aim of this study was to compare postoperative complication rates after restorative proctocolectomy with and without previous IFX therapy for medical refractory UC. For this purpose, 1- and 2 stage procedures were analyzed separately.

2. Materials and methods

For the purpose of this retrospective comparative study, patients requiring restorative proctocolectomy for medical refractory UC between January 1st 2006 and January 1st 2010 were retrieved from our institutional registries of all IPAA procedures. All patients were included, irrespective of the degree of colitis. Patients who underwent surgery because of dysplasia or malignancy were excluded.

Primary endpoints were the total complication rate within 30 days after surgery, the number of all infectious complications, the number of patients with pelvic sepsis and the number of non-infectious complications in patients with and without previous IFX therapy. Secondary endpoints were the direct postoperative hospital stay (PHS) and total postoperative hospital stay (THS), defined as PHS plus the additional hospitalization period if patients were readmitted within 30 days after surgery.

An infectious complication was defined as a complication leading to any kind of inflammation, including pelvic sepsis, surgical site infection, intra-abdominal abscesses and infectious complications other than abdominal. Pelvic sepsis was defined as anastomotic leakage, requiring reoperation and temporary ileostomy or presacral abscesses that could be treated percutaneously. Only clinically apparent pelvic sepsis was included. To detect pelvic sepsis, CRP measurements were routinely taken postoperatively and a CT scan was done at the slightest suspicion of leakage.

Non-infectious complications were all complications that did not meet the qualification of infectious complication. These included complications such as paralytic ileus, bleeding, dehydration, electrolyte disturbances, urinary retention or peroperative side damage.

All medical charts were reviewed. Patient characteristics were collected, as well as UC specific data. These disease specific characteristics included disease duration, extent of disease and preoperative medical therapy other than IFX. In case of previous IFX therapy, the time interval between last infusion and surgery and number of infusions were assessed. In patients who underwent a 2-stage procedure, time between acute colectomy and completion proctectomy with IPAA was determined.

In our hospital, a step-up treatment algorithm is applied for treatment of ulcerative colitis. Therefore, IFX was always applied as second line therapy in case of steroid refractory or dependent disease. In case surgery is needed, the preoperative condition was optimized by means of a short course of steroids, to lower levels of inflammation.

One-stage procedure and 2-stage procedures, both with or without temporary ileal diversion were analyzed separately. In the definitions we used, a procedure was defined a 1-stage procedure if proctocolectomy and creation of pouch were performed in one single operation, and also if a temporary ileostomy was created (this did not exclude patients from the 1-stage group). In all 2-stage procedure cases, an emergency resection was performed as the first stage, and a rest proctectomy with creation of pouch was done later as the second stage. Again, temporary ileostomies were performed in some, not excluding them from the 2-stage group.

A 2-stage procedure was performed in patients with an acute medical refractory exacerbation of UC requiring emergency colectomy. One-stage procedures were performed electively in patients with refractory disease without signs of acute disease activity. A temporary ileostomy was not routinely performed in all patients, but only in those considered to be at high risk of developing postoperative anastomotic leakage. Risk factors were considered steroids>20 mg/day, severe proctitis, difficult procedure or incomplete donuts.

Within these two groups, other variables potentially related to the postoperative complication rates apart from IFX were analyzed. These were smoking, a temporary stoma, ASA classification, and steroids and immunomodulatory therapy within 3 months preoperatively. In case of a significant association, the effect of IFX was adjusted for these variables.

To detect differences between the patients in the 1-stage and 2-stage groups at time of pouch reconstruction, irrespective of IFX therapy, the two groups were compared with regard to the demographic and clinical characteristics and the surgical outcome.

2.1. Statistical analysis

Data are presented as median with inter quartile range (IQR). To provide a quantitative impression of the size of the effect of IFX and potential confounding factors, analysis of complications (total, infectious, anastomotic leakage and non infectious) was performed by calculating the risk difference (Δ%) with 95% confidence interval (CI). Additionally, p-values were calculated using chi-squared tests. If confounding factors were found, adjustment was made using multivariate regression analysis in case of sufficient cases to be able to perform multivariable analysis, presented as odds ratio (OR) with the 95% CI.

Statistical analysis was performed by using SPSS® software version 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

During the study period, 117 pouch procedures were performed. Forty-five patients had a primary disease other than UC: familial adenomatous polyposis (30), dysplasia or carcinoma in the presence of UC (11), Crohn's disease (3), and slow transit obstipation syndrome (1). Of the remaining 72 patients, 33 patients underwent a 1-stage procedure and 39 patients underwent a 2-stage procedure. Most of the 1-stage patients were operated laparoscopically, and the 2-stage patients were operated via a Pfannenstiehl incision. Patients who did not have a defunctioning ileostomy had a pouch drain until the 6th postoperative day. Thereafter they could only be discharged if the daily number of bowel movements was acceptable.

3.1. One-stage procedure

Of the 33 patients undergoing a 1-stage procedure, 21 patients received previous IFX therapy. Median number of infusions was 5 (IQR 3–6), and median time between last infusion and operation was 7 months (IQR 2.6–8.3). Six patients had their last IFX administration within 3 months before surgery. Table 1 shows the characteristics of the IFX and non-IFX patients. No significant differences between these patients were found. All patients who underwent a 1-stage procedure were in-between exacerbations.

Fig. 1 shows the complications after a 1-stage procedure with and without prior IFX therapy. Total and infectious complications were not significantly different. However more IFX-treated patients had pelvic sepsis (anastomotic leakage (4) and presacral abscess (1), thus total 5/21 vs. 0/12; risk difference (RD) 24%; 95% CI: 6 to 42, p=0.067) and more non-infectious complications (8/21 vs. 1/12; RD 30%; 95% CI: 4 to 56, p=0.065).

Table 2 shows characteristics of the 5 patients with pelvic sepsis after a 1-stage procedure. Time between last IFX administration and surgery was <3 months in 2 of the 5 patients with pelvic sepsis. Two of the other three patients had an interval of 7 months and one patient had an interval of 5 months between last administration of IFX and surgery. Two of the patients received a primary temporary ileostomy during the proctocolectomy with IPAA procedure.

By analyzing other potentially predictive factors, smoking turned out to be significantly associated with a higher total complication rate (5/6 from the patients who smoked

Table 1 Patient characteristics of patients from the 1-stage group with and without prior IFX therapy.

	IFX: N=21	No IFX: N=12	p
Gender (male)	12 (57%)	7 (58%)	0.947
Age at time of surgery	35.1 (24.6–45.0)	34.4 (29.8–42.6)	0.895
Smoking (yes)	5 (24%)	1 (8%)	0.370
BMI	23.0 (20.2–25.3)	21.9 (20.6–27.2)	0.552
Temporary ileostomy	6 (29%)	7 (58%)	0.150
Disease duration [a]	42.0 (26.6–59.1)	54.4 (29.1–139.0)	0.392
Location of disease			
- Pan colitis	15 (71%)	6 (50%)	0.260
- Left sided	5 (23%)	6 (50%)	
- Proctitis	1 (5%)	0	
Medication<3 months			
- Steroids	13 (62%)	9 (75%)	0.443
- AZA/6MP	13 (62%)	8 (67%)	0.784
- 5-aminosalycates	16 (76%)	8 (67%)	0.555
- Cyclosporine	2 (10%)	2 (17%)	0.545
- Time IFX-surgery [a]	7.1 (2.6–8.3)		
No of IFX infusions	5 (3–6)		

[a] In months. Data: absolute numbers (percentage) or medians (inter quartile range).

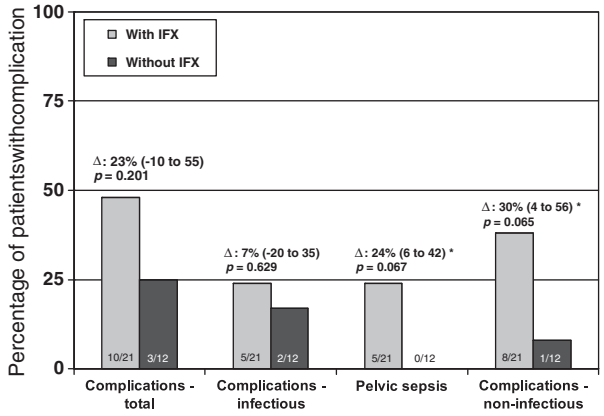

Figure 1 Complications after 1-stage procedure with and without previous IFX therapy.

vs. 8/27 in the non-smokers group had a complication, Δ% 54; 95%CI 19–88). The infectious complications were not affected by any variable. Apart from IFX, no other factors influenced the rate of pelvic sepsis. Non-infectious complications were, apart from IFX, influenced by smoking (4/6 vs 5/27, Δ% 48; 95%CI 8–89) and an ASA classification of 3 as compared to an ASA classification of 1 (ASA 1: 1/9 vs. ASA 3: 3/5, Δ% 49; 95%CI −97 to −1).

Due to the small number of non-infectious complications, adjustment for these confounders could not be performed.

PHS was 9 days (IQR: 7–11) in the IFX group and 9 days (IQR: 7–10) in the non IFX group (mean difference: 0.4 days, (95% CI −4.5 to 3.6)). THS was 10 days (IQR 8–15) and 9 days (IQR 7–14) in the IFX and non-IFX groups, respectively (mean difference 2.2 days, (95% CI −7.3 to 2.8)). Reasons for readmission were nausea, ileus, dehydration and anastomotic leakage. In the 1-stage group, ten patients were readmitted, of whom 4 were readmitted only one night for observation.

3.2. Two-stage procedure

Thirty-nine patients underwent a 2-stage procedure. Of these, 17 patients had received IFX and 22 patients did not. In this IFX group, median number of infusions was 2 (IQR 1–3), and median time between last infusion and operation was 12 months (IQR 7–16). Table 3 shows the characteristics of the patients who underwent a 2-stage procedure. There were several differences in baseline characteristics in the 2-stage group between the patients with and without IFX therapy: the non-IFX group had a significantly higher proportion of male patients, higher median age, higher median BMI, and a higher percentage of temporary ileostomy.

Fig. 2 shows the complication rates after the 2-stage procedure with and without prior IFX therapy. No differences between IFX and non-IFX patients were found with regard to total complications, infectious complications, anastomotic leakage and non-infectious complications. In the IFX group, 3 patients suffered from pelvic sepsis (2 had anastomotic leakage and one had a presacral abscess). In the non-IFX group, 4 patients suffered from pelvic sepsis (2 had anastomotic leakage and 2 had a presacral abscess drained percutaneously). Table 4 shows characteristics of these 7 patients.

The 4 characteristics that were different between the IFX and non-IFX groups (gender, BMI, age and temporary stoma) did not affect the postoperative complication rates. Also the other pre-defined factors investigated (including smoking and ASA classification) showed no association with any of the complication categories.

PHS was 9 days (IQR: 8–10) in the IFX group and 8 days (IQR: 7–11) in the non IFX group (mean difference: 1.1 days, (95% CI −4.3 to 6.4)). THS was 9 days (IQR 8–12) and 9 days (IQR 8–12) in the IFX and non-IFX groups, respectively (mean difference 1.5 days (95% CI −4.7 to 7.7)). Reasons for readmission in these patients were bleeding and anastomotic leakage. In the 2-stage group, seven patients required readmission.

3.3. Comparison of 1-stage group and 2-stage group (Table 5)

When comparing the 1-stage and 2-stage groups, more patients from the 2-stage group had pan colitis requiring a procedure in two stages, while more patients from the 1-stage group have used medication (including IFX) within 3 months

Table 2 Characteristics of 5 patients with pelvic sepsis after 1-stage procedure.

	Patient 1 Leakage	Patient 2 Leakage	Patient 3 Leakage	Patient 4 Leakage	Patient 5 Abscess
Gender	M	M	M	M	M
Age	46.7	46.4	18.9	27.6	40.6
BMI	21.5	28.1	23.6	23.0	22.1
Smoking	–	–	–	+	+
Temp ileostomy	–	–	+	+	+
Disease location	Pan colitis	Pan colitis	Pan colitis	Pan colitis	Pan colitis
Med <3 months	Steroids; Azathioprine; Mesalazine	–	Steroids	–	Steroids; Azathioprine;
		Azathioprine; Mesalazine;	–	Azathioprine; Mesalazine;	–
	–	IFX	–	IFX	–
IFX Y/N	Yes	Yes	Yes	Yes	Yes
Time IFX–pouch	7 months	2.6 months	7 months	1.5 months	5.1 months
No. of infusions	8	2	14	5	6

Temp = temporary; med = medication used within 3 months before surgery; no. = number.

Table 3 Patient characteristics of patients from the 2-stage group with and without prior IFX therapy.

	IFX: N = 17	No IFX: N = 22	Δ%/mean Δ (95%CI)
Gender (male)	6 (35%)	16 (73%)	0.019
Age at time of surgery	35.7 (26.1–41.5)	41.0 (37.0–48.0)	0.034
Smoking (yes)	2 (12%)	4 (18%)	0.582
BMI	23.1 (19.6–25.7)	25.5 (22.8–27.8)	0.060
Temporary ileostomy	1 (6%)	8 (36%)	0.025
Disease duration [a]	42.0 (26.6–59.1)	54.4 (29.1–139.0)	0.001
Location of disease			0.489
- Pan colitis	15 (88%)	20 (91%)	
- Left sided	2 (12%)	2 (9%)	
Medication <3 months			
- Steroids	0	1 (5%)	1.000
- AZA/6MP	1 (6%)	2 (9%)	1.000
- 5-aminosalycates	1 (6%)	3 (14%)	0.624
Time IFX-surgery [a]	11.8 (7.3–15.5)		
No of IFX infusions	2 (1–3)		

[a] In months. Data: absolute numbers (percentage) or medians (inter quartile range).

before surgery, as was expected. Furthermore, there was a non-significant higher rate of defunctioning ileostomies in the 2-stage group. The complication rates were similar in the two groups.

4. Discussion

In this patient series, IFX did not influence the total number of complications after restorative proctocolectomy for medical refractory UC. However, after a 1-stage procedure, a higher number of pelvic sepsis and more non-infectious complications were observed in the patients who had received IFX. After a 2-stage procedure, no significant differences were found. Therefore, the results of this small study support a 2-stage procedure in patients with prior IFX therapy.

The majority of patients received their last IFX infusion > 3 months before the proctocolectomy with IPAA. This includes three of the patients with pelvic sepsis in the 1-stage procedure group (the IFX-surgery interval was 5 months in 1 and 7 months in two). Two studies that evaluated postoperative complications in IFX treated UC patients used a 90 days interval as cut off value.[2,9,10] Other studies also included patients with a larger preoperative IFX-free interval, similar to our study.[3–5] Pharmacokinetic data of IFX shows that levels of IFX are detectable over a mean period of 12 weeks, but this can be up to a maximum of 28 weeks.[11,12] Although the therapeutic effect of anti-TNF treatment at these larger intervals is probably small, the biological effect may be significant for a period up to 28 weeks. In other words, it might be possible that anti-TNF monoclonal antibodies will remain capable of affecting postoperative recovery even after 90 days.[5] Whether one should take all patients with IFX into account or only those with IFX within 3 months before surgery remains to be determined in pooled analyses of larger patient series. In our cohort of 1-stage procedures, there were no statistical differences when comparing those with IFX within 3 months (n = 6) to patients without IFX or IFX > 3 months before surgery.

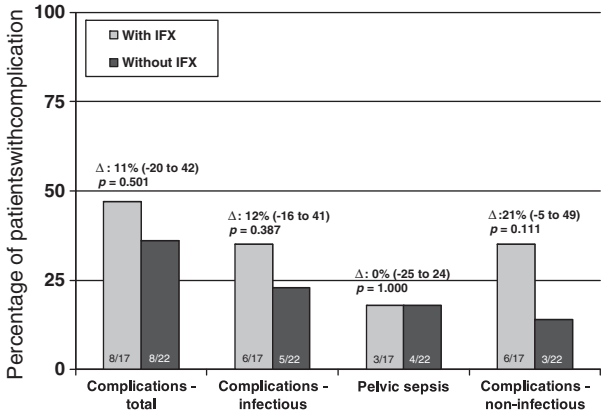

Figure 2 Complications after 2-stage procedure with and without previous IFX therapy.

Several important factors were not normally distributed between the IFX and non IFX groups. This might have influenced the results. Importantly, in both the 1-stage group and the 2-stage group, the non-IFX groups had more deviating ileostomies. In the small groups presented in this study, this discrepancy did not influence any of the complication categories as a confounder. When looking separately at the patients from the 1-stage group who received a temporary deviating stoma (n = 13), pelvic sepsis only occurred in 3 of the 6 IFX treated patients (50%), versus none of the 7 patients without IFX. Therefore a temporary ileostomy might not preclude the risk of pelvic sepsis. In the 1-stage group, besides IFX, there were some factors that also influenced the higher rate of non-infectious complications. These confounders were smoking and an ASA classification of 3. The small numbers in this study precluded adjustment for these confounding factors. Analysis of confounding factors should be assessed in a meta-analysis of larger datasets.

We compared the 1- and 2-stage groups irrespective of IFX therapy. This showed a higher rate of pan colitis patients in the 2-stage group. This was to be expected, since patients

Table 4 Characteristics of 7 patients with pelvic sepsis after 2-stage procedure.

	Patient 1 Leakage	Patient 2 Leakage	Patient 3 Leakage	Patient 4 Leakage	Patient 5 Abscess	Patient 6 Abscess	Patient 7 Abscess
Gender	F	F	F	M	F	M	F
Age	39.3	35.7	40.4	53.9	35.0	42.4	28.4
BMI	26.0	19.2	24.6	25.5	25.3	27.7	20.3
Complications at colectomy	No	No	No	Platzbauch	No	No	No
Temp ileostomy	–	–	–	+	–	+	+
Disease location	Pan colitis	Pan colitis	Pan colitis	Pan colitis	Pan colitis	Pan colitis	Pan colitis
Med<3 months	–	–	Mesalazine	–	–	–	–
IFX Y/N	Yes	Yes	No	No	Yes	No	No
Time IFX-pouch [a]	11.5	25.9			11.77		
No. of infusions	1	3			13		

[a] In months; temp = temporary; med = medication used within 3 months before surgery; no. = number.

with pan colitis more often require an emergency colectomy as compared to patients with proctitis or left sided colitis. In the demographics no differences were found indicating that the 2-stage patients would have an inferior outcome, although the 2-stage patients had a non-significant lower rate of defunctioning ileostomies. Complications in the two groups were similar. At the time of emergency colectomy the 2-stage group patients were sicker as compared to the patients from the 1-stage group, a reason why these patients received the procedure in two stages. However, at time of pouch reconstruction the two groups were comparable for most demographics.

Several centers have published their results with regard to IFX therapy and postoperative complication rates after restorative proctocolectomy with IPAA in UC patients. Mor et al.[5] found IFX, administered at a median of 13.5 weeks preoperatively (IQR, 4–37 weeks), to be associated with an increased total postoperative complication rate, while several other studies found no differences.[3–5,9,10,13] With regard to pelvic sepsis and infectious complications, 2 studies

Table 5 Comparison between all patients from the 1-stage group and 2-stage groups.

	1-stage total (n=33)	2-stage total (n=39)	p-value
Demographics			
Gender (male)	19 (58%)	22 (56%)	0.921
Age at time of surgery	35.1 (27.0–43.3)	39.9 (33.7–44.3)	0.237
Smoking (yes)	6 (18%)	6 (15%)	0.751
BMI	22.5 (20.6–25.7)	24.6 (21.5–26.8)	0.229
Temporary ileostomy	13 (39%)	9 (23%)	0.134
Clinical variables			
Disease duration[a]	42.8 (28.2–82.7)	53.7 (23.3–105.9)	0.237
Location of disease			0.022
- Pan colitis	21 (64%)	35 (90%)	
- Left sided	11 (33%)	4 (10%)	
- Proctitis	1 (3%)	–	
Medication<3 months			
- Steroids	22 (67%)	1 (3%)	0.000
- AZA/6MP	21 (64%)	3 (8%)	0.000
- 5-aminosalycates	24 (73%)	4 (10%)	0.000
- Cyclosporines	4 (12%)	–	0.042
Time IFX-surgery*	7.1 (2.6–8.3)	11.8 (7.3–15.5)	0.014
No of IFX infusions	5 (3–6)	2 (1–3)	0.001
Surgical outcome			
Complications total	13 (39%)	16 (41%)	0.888
Complications infectious	7 (21%)	11 (28%)	0.495
Pelvic sepsis	5 (15%)	7 (18%)	0.751
Complications non-infectious	9 (27%)	9 (23%)	0.682

found significant associations with IFX therapy[4,5] and 5 found no differences.[2,3,9,10,13]

Mor et al. primarily analyzed the postoperative complication rates after a 1-stage procedure (in their terminology this procedure is called a 2 stage procedure, because all patients received a temporary ileostomy; restoration of continuity was named the second stage of the operation).[5] In this 1-stage comparison, they found a significant increase of both total complications (OR 3.54, p=0.04) and sepsis (OR13.8, p-0.011). A secondary outcome of their study was the *requirement* of a 2-stage procedure (in their terminology; a 3-stage procedure), which was significantly increased in patients with previous IFX therapy as compared with non-IFX patients. In this context, the fact that our study promotes a 2-stage procedure is in line with their results: in retrospect they concluded that IFX might have altered their surgical approach, unaware of this during treatment of the individual patients. Next, they found increased septic complications in the 1-stage group. In reaction to this publication, Bordeianou et al. also studied whether IFX use affected the rate of emergency surgery, subtotal colectomies and ileo-anal J pouch reconstructions.[14] The authors found no increased rate of multistep procedures in their IFX-treated patients. The remaining studies did not separately analyze the 1- and 2-stage procedure patients.

A meta-analysis that includes most of these studies[2–5,13] was recently performed by Yang et al.[15] After pooling the data, a significantly increased total complication rate was found in patients with previous IFX treatment.[15] Sub-analyses on infectious and non-infectious complications were not different compared with patients without IFX therapy. The authors concluded that preoperative IFX therapy enlarges the risk for postoperative complications. Furthermore, they concluded that there was insufficient power for sub-group analyses, but that there was a trend to more infectious complications.

A shortcoming of this study is the small sample size of this study. The fact that this study has a too small sample size to draw valid conclusions can be retrieved from the fact that the association we found between IFX therapy and pelvic sepsis in the 1-stage group, by calculating risk differences with 95% CI, is fragile and could not be confirmed by chi squared testing. The study however shows a trend that IFX-treated patients might benefit from a 2-stage approach. Furthermore, the retrospective design of the study implies a selection bias is present. It must be noted that the patients from the 1-stage group and patients from the 2-stage group are two different groups of patients. When comparing the patient characteristics from the 1- and 2-stage groups, there were more patients in the 2-stage group who had pan colitis. The fact that these patients received less IFX infusions shows that these patients had a reduced response to IFX. These patients subsequently required the next step, being surgery. Since inflammation was insufficiently scaled down due to failed IFX therapy, an emergency colectomy was performed as a first stage in these patients.

Whether IFX is a true risk factor for increased postoperative complication rates remains to be determined in larger meta-analyses including more patient series. Although the present patient series is only small (as indicated by the wide confidence intervals) and can merely enlarge the data pool in literature, the outcomes of this small study support a 2-stage procedure in patients with prior IFX therapy.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Acknowledgments

Author contributions:

Emma J Eshuis: planning and design of study, collecting data, statistical analysis, analysis and interpretation of data, drafting the manuscript, and approval of the final draft submitted.

Rana L Al Saady: planning the study, collecting data, statistical analysis, and approval of the final draft submitted.

Pieter CF Stokkers: treated studied patients, interpreting data, drafting manuscript, and approval of the final draft submitted.

Cyriel Y Ponsioen: treated studied patients, interpreting data, drafting manuscript, and approval of the final draft submitted.

Pieter J Tanis: treated studied patients, interpreting data, drafting manuscript, and approval of the final draft submitted.

Willem A Bemelman: planning study, treated studied patients, interpreting data, drafting manuscript, and approval of the final draft submitted.

References

1. Gisbert JP, Gonzalez-Lama Y, Mate J. Systematic review: infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007;**25**:19–37.
2. Ferrante M, D'Hoore A, Vermeire S, Declerck S, Noman M, Van Assche G, et al. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009;**15**:1062–70.
3. Schluender SJ, Ippoliti A, Dubinsky M, Vasiliauskas EA, Papadakis KA, Mei L, et al. Does infliximab influence surgical morbidity of ileal pouch-anal anastomosis in patients with ulcerative colitis? *Dis Colon Rectum* 2007;**50**:1747–53.
4. Selvasekar CR, Cima RR, Larson DW, Dozois EJ, Harrington JR, Harmsen WS, et al. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg* 2007;**204**:956–62.
5. Mor IJ, Vogel JD, da Luz MA, Shen B, Hammel J, Remzi FH. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008;**51**:1202–7.
6. Travis SP, Stange EF, Lémann M, Oresland T, Bemelman WA, Chowers Y, et al. European evidence-based consensus on the management of ulcerative colitis: Current management. *J Crohns Colitis* 2008;**2**:24–62.
7. Williamson ME, Lewis WG, Sagar PM, Holdsworth PJ, Johnston D. One-stage restorative proctocolectomy without temporary ileostomy for ulcerative colitis: a note of caution. *Dis Colon Rectum* 1997;**40**:1019–22.
8. Hueting WE, Buskens E, van der Tweel I, Gooszen HG, van Laarhoven CJ. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients. *Dig Surg* 2005;**22**:69–79.
9. Kunitake H, Hodin R, Shellito PC, Sands BE, Korzenik J, Bordeianou L. Perioperative treatment with infliximab in p
atients with Crohn's disease and ulcerative colitis is not

associated with an increased rate of postoperative complications. *J Gastrointest Surg* 2008;**12**:1730–6.
10. Gainsbury ML, Chu DI, Howard LA, Coukos JA, Farraye FA, Stucchi AF, et al. Preoperative infliximab is not associated with an increased risk of short-term postoperative complications after restorative proctocolectomy and ileal pouch-anal anastomosis. *J Gastrointest Surg* 2011;**15**:397–403.
11. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. *Nat Rev Immunol* 2003;**3**:745–56.
12. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* 2008;**117**:244–79.
13. Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005;**128**:1805–11.
14. Bordeianou L, Kunitake H, Shellito P, Hodin R. Preoperative infliximab treatment in patients with ulcerative and indeterminate colitis does not increase rate of conversion to emergent and multistep abdominal surgery. *Int J Colorectal Dis* 2010;**25**:401–4.
15. Yang Z, Wu Q, Wu K, Fan D. Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2010;**31**:486–92.