Treatment of inflammatory bowel disease: medical and surgical aspects
Eshuis, E.J.

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Previous infliximab therapy and post-operative complications after proctocolectomy with ileal pouch anal anastomosis (IPAA)

Emma J. Eshuis
Rana L. Al Saady
Pieter C.F. Stokkers
Cyriel Y. Ponsioen
Pieter J. Tanis
Willem A. Bemelman

Submitted
ABSTRACT

Introduction
The aim was to compare complication rates after ileal pouch anal anastomosis in refractory ulcerative colitis patients with versus without previous infliximab therapy.

Methods
Retrospectively, all patients who underwent a pouch procedure for medical refractory ulcerative colitis between January 2006 and January 2010 were selected. Post-operative complications, infliximab use and time interval between last infliximab administration and restorative surgery were assessed. One-stage procedures (proctocolectomy with ileal pouch anal anastomosis) and 2-stage procedures (emergency colectomy and subsequent completion proctectomy with ileal pouch anal anastomosis) were analysed separately.

Results
Seventy-two patients were included; 33 underwent a 1-stage procedure and 39 had a 2-stage procedure. In the 1-stage group, 21 patients (64%) had previous infliximab therapy; median time between last infusion and surgery was 7.1 months (inter quartile range 2.6-8.3). Infliximab-treated patients had a higher incidence of pelvic sepsis (5/21 versus 0/12; risk difference 24%; 95% confidence interval 6 to 42) and non-infectious complications (8/21 versus 1/12; RD 30%; 95% confidence interval: 4 to 56). In the 2-stage group, 17 patients (44%) had previous infliximab therapy; median time between last infusion and pouch surgery was 11.8 (inter quartile range 7.3-15.5) months. Total, infectious and non-infectious complication rates as well as the number of patients with pelvic sepsis were similar for infliximab and non-infliximab patients in the 2-stage group.

Conclusion
This small study suggests that infliximab use prior to a 1-stage restorative proctocolectomy in patients with ulcerative colitis is associated with an increased incidence of pelvic sepsis. A 2-stage procedure in these patients should be considered.
INTRODUCTION

Steroid dependent ulcerative colitis (UC) can medically be treated with infliximab (IFX), a monoclonal antibody directed against the inflammatory cytokine TNF-alpha. 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 post-operative complications.

UC that is refractory to all medical therapies should be treated surgically by means of a proctocolectomy with ileal pouch anal anastomosis (IPAA). 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. Both approaches can be performed with or without temporary ileal diversion.

Direct post-operative 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. It is therefore of first importance to minimize the need for surgery. If surgery is required, the risk of post-operative complications should be minimized.

If IFX therapy shortly before restorative surgery is associated with higher morbidity jeopardizing long-term pouch function, a 2-stage procedure is preferable to a 1-stage procedure. Extending the period between last administration of IFX therapy and pouch surgery probably lowers the complication risk. Therefore, the aim of this study was to compare post-operative complication rates after restorative proctocolectomy with and without previous IFX therapy for medical refractory UC. For this purpose, 1- and 2 stage procedures were analysed separately.

PATIENTS 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.

Primary end points 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 end points were the direct post-operative hospital stay (PHS) and total post-operative 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. Pelvic sepsis was defined as anastomotic leakage requiring reoperation and temporary ileostomy, or presacral abscesses that could be treated percutaneously. Non-infectious complications were all complications that did not meet the qualification of infectious complication.
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.

One-stage procedure and 2-stage procedures, both with or without temporary ileal diversion were analysed separately. 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.

Within these two groups, other variables potentially related to the post-operative complication rates apart from IFX were analysed. These were smoking, a temporary stoma, American Society of Anesthesiologists (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.

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, pelvic sepsis and non-infectious) was performed by calculating the risk difference (RD, Δ%) with 95% confidence interval (CI). If confounding factors were found, adjustment was made using multivariate regression 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).

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.

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.
Figure 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; RD 24%; 95% CI: 6 to 42) and more non-infectious complications (8/21 vs. 1/12; RD 30%; 95% CI: 4 to 56).

**TABLE 1: PATIENT CHARACTERISTICS OF PATIENTS FROM THE 1-STAGE GROUP WITH AND WITHOUT PRIOR IFX THERAPY**

<table>
<thead>
<tr>
<th></th>
<th>IFX: N=21</th>
<th>No IFX: N=12</th>
<th>Δ% / mean Δ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>12 (57%)</td>
<td>7 (58%)</td>
<td>1% (-36.2 to 33.8)</td>
</tr>
<tr>
<td>Age at time of surgery</td>
<td>35.1 (24.6–45.0)</td>
<td>34.4 (29.8–42.6)</td>
<td>1.93 (-6.8 to 10.4)</td>
</tr>
<tr>
<td>Smoking (yes)</td>
<td>5 (24%)</td>
<td>1 (8%)</td>
<td>16% (-8.5 to 39.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.0 (20.2–25.3)</td>
<td>21.9 (20.6–27.2)</td>
<td>0.69 (-1.8 to 3.2)</td>
</tr>
<tr>
<td>Temporary ileostomy</td>
<td>6 (29%)</td>
<td>7 (58%)</td>
<td>29% (-63.7 to 4.2)</td>
</tr>
<tr>
<td>Disease duration*</td>
<td>42.0 (26.6–59.1)</td>
<td>54.4 (29.1–139.0)</td>
<td>35.3 (-5.5 to 76.1)</td>
</tr>
<tr>
<td>Location of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan colitis</td>
<td>15 (71%)</td>
<td>6 (50%)</td>
<td>21% (-12.8 to 55.7)</td>
</tr>
<tr>
<td>Left sided</td>
<td>5 (23%)</td>
<td>6 (50%)</td>
<td>27% (-59.8 to 7.5)</td>
</tr>
<tr>
<td>Proctitis</td>
<td>1 (5%)</td>
<td>0</td>
<td>5% (-4.4 to 13.9)</td>
</tr>
<tr>
<td>Medication &lt;3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>13 (62%)</td>
<td>9 (75%)</td>
<td>13% (-45.2 to 19.0)</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>13 (62%)</td>
<td>8 (67%)</td>
<td>5% (-38.6 to 29.0)</td>
</tr>
<tr>
<td>5-aminosalycates</td>
<td>16 (76%)</td>
<td>8 (67%)</td>
<td>9% (-22.8 to 41.8)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2 (10%)</td>
<td>2 (17%)</td>
<td>7% (-31.7 to 17.4)</td>
</tr>
<tr>
<td>Time IFX - surgery*</td>
<td>7.1 (2.6 – 8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of IFX infusions</td>
<td>5 (3-6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* in months. Data are presented as absolute numbers with percentages or as medians with the inter quartile range.

**FIGURE 1: COMPLICATIONS AFTER 1-STAGE PROCEDURE WITH AND WITHOUT PREVIOUS IFX THERAPY**
Table 2 shows characteristics of the five patients with pelvic sepsis after a one-stage procedure. Time between last IFX administration and surgery was < 3 months in two of the five 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 analysing other potentially predictive factors, smoking turned out to be significantly associated with a higher total complication rate (5/6 from the patients who smoked 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).

**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:

<table>
<thead>
<tr>
<th>Patient 1 Leakage</th>
<th>Patient 2 Leakage</th>
<th>Patient 3 Leakage</th>
<th>Patient 4 Leakage</th>
<th>Patient 5 Abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>46.7</td>
<td>46.4</td>
<td>18.9</td>
<td>27.6</td>
</tr>
<tr>
<td>BMI</td>
<td>21.5</td>
<td>28.1</td>
<td>23.6</td>
<td>23.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Temporary ileostomy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Disease location</td>
<td>Pan colitis</td>
<td>Pan colitis</td>
<td>Pan colitis</td>
<td>Pan colitis</td>
</tr>
<tr>
<td>Medication &lt;3 months</td>
<td>steroids azathioprine mesalazine</td>
<td>- azathioprine mesalazine</td>
<td>steroids -</td>
<td>azathioprine mesalazine</td>
</tr>
<tr>
<td>IFX Y/N</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Time IFX – pouch*</td>
<td>7 months</td>
<td>2.6 months</td>
<td>7 months</td>
<td>1.5 months</td>
</tr>
<tr>
<td>Number of infusions</td>
<td>8</td>
<td>2</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

* in months
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.

Figure 2 shows the complications 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, pelvic sepsis and non-infectious complications. In the IFX group, three patients suffered from pelvic sepsis (two had

| 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%) | 38% (-67 to -8) |
| Age at time of surgery | 35.7 (26.1 – 41.5) | 41.0 (37.0 – 48.0) | 8.6 (1.3 to 15.9) |
| Smoking (yes) | 2 (12%) | 4 (18%) | 6% (-29 to 16) |
| BMI | 23.1 (19.6 – 25.7) | 25.5 (22.8 – 27.8) | 2.3 (0.1 to 4.5) |
| Temporary ileostomy | 1 (6%) | 8 (36%) | 30% (-54 to -8) |
| Disease duration* | 42.0 (26.6 – 59.1) | 54.4 (29.1–139.0) | 35.3 (-5.5 to 76.1) |
| Location of disease | | | |
| Pan colitis | 15 (88%) | 20 (91%) | 3% (-22 to 17) |
| Left sided | 2 (12%) | 2 (9%) | 3% (-17 to 22) |
| Medication <3 months | | | |
| Steroids | 0 (6%) | 1 (5%) | 5% (-13 to 4) |
| AZA/6MP | 1 (6%) | 2 (9%) | 3% (-14 to 13) |
| 5-aminosalycates | 1 (6%) | 3 (14%) | 8% (-26 to 10) |
| Time IFX - surgery* | 11.8 (7.3 – 15.5) | | |
| Number of IFX infusions | 2 (1 – 3) | | |

* in months. Data are presented as absolute numbers with percentages or as medians with the inter quartile range.
anastomotic leakage and one had a presacral abscess). In the non-IFX group, four patients suffered from pelvic sepsis (two had anastomotic leakage and two had a presacral abscess drained percutaneously). Table 4 shows characteristics of these seven patients.

The 4 characteristics that were different between the IFX and non-IFX groups (gender, BMI, age and temporary stoma) did not affect the post-operative complication rates. Also the pre-defined other 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).

| 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                | M                | 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 colectomy                       | no               | no               | no               | platzbauch       | no               | no               | no               |
| Temporary ileostomy                           | -                | -                | -                | +                | -                | +                | +                |
| Disease location                              | Pan colitis      | Pan colitis      | Pan colitis      | Pan colitis      | Pan colitis      | Pan colitis      | Pan colitis      |
| Medication <3 months                          | -                | -                | mesalazine       | -                | -                | -                | -                |
| IFX Y/N                                       | yes              | yes              | no               | no               | yes              | no               | no               |
| Time IFX – pouch*                             | 11.5             | 25.9             |                   |                   | 11.77            |                   |                   |
| Number of infusions                           | 1                | 3                |                   |                   | 13               |                   |                   |

* in months

**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 one and 7 months in two). Three studies that evaluated post-operative 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 post-operative recovery even after 90 days. 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 differences when comparing those with IFX within 3 months (n=6) to patients without IFX or IFX > 3 months before surgery.

In both the 1-stage group and the 2-stage group, the non-IFX groups had more deviating ileostomies. This discrepancy did not influence any of the complication categories as a confounder. 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.

Another potential confounder that could not be corrected for but should be considered in interpretation of the data is the severity of the disease. Conceivably, patients with previous IFX therapy received this therapy because of more severe disease compared to patients without IFX. This might have influenced the post-operative recovery. However, the vast majority of IFX treated patients had stopped this treatment > 3 months before surgery. It is therefore unlikely that prior IFX use reflected more severe disease at time of surgery.

Several centres have published their results with regard to IFX therapy and post-operative complication rates after restorative proctocolectomy with IPAA in UC patients. Mor et al. found IFX, administered at a median of 13.5 weeks preoperatively (IQR, 4–37 weeks), to be associated with an increased total post-operative complication rate, while several other studies found no differences. With regard to pelvic sepsis and infectious complications, 2 studies found significant associations with IFX therapy and 5 found no differences. Mor et al. primarily analysed the post-operative 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). In this 1-stage comparison, they found a significant increase of both total complications (OR 3.54, p = 0.040) and sepsis (OR 13.8, 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 ileoanal J pouch reconstructions. The authors found no increased rate of multistep procedures in their IFX-treated patients. The remaining studies did not separately analyse the 1- and 2-stage procedure patients.

A meta-analysis that includes most of these studies was recently performed by Yang et al. After pooling the data, a significantly increased total complication rate was found in patients with previous IFX treatment. 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 post-operative complications. Furthermore, they concluded that there was insufficient power for subgroup analyses, but that there was a trend to more infectious complications. Whether IFX is a true risk factor for increased post-operative 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.
REFERENCE LIST


