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

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Ten years of infliximab for Crohn’s disease: outcome in 469 patients from two tertiary referral centres

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Submitted
ABSTRACT

Introduction
Aim was to assess the long-term effectiveness of infliximab therapy in Crohn’s disease patients treated in cohorts from two third-line referral centres.

Patients and methods
All consecutive Crohn’s disease patients treated with infliximab were assessed. Medical charts were retrospectively reviewed. End points were primary therapeutic effectiveness, sustained benefit, effectiveness of retreatment, surgical intervention rate before and after infliximab therapy and safety of therapy.

Results
A total of 488 patients received infliximab. For 469 patients (96%) it was possible to assess effectiveness. Median length of follow-up was 4.5 year (inter quartile range: 2.7 – 6.8). Seventy patients (15%) had an unsuccessful remission induction course. A total of 316 patients received maintenance therapy. A successful scheduled maintenance regimen was documented in 169/276 (61%). Episodic maintenance therapy was successful in 19/40 patients (48%). Estimated 5-year sustained benefit was 55.7% (95% confidence interval: 48.8 – 62.6). Concomitant immunosuppression and younger age at diagnosis were associated with improved sustained benefit of infliximab. A second course of infliximab after previous discontinuation was seen in 131 patients. Similar effectiveness rates were noted. Twenty seven of 59 patients (46%) who failed on infliximab therapy showed response to a second infliximab-episode. The rate of abdominal surgical interventions per 100 patient years was significantly reduced after infliximab initiation in the 276 patients treated with a scheduled maintenance regime (reduction: 2.70 (95% confidence interval: -4.82 to -0.35; p = 0.018). Mortality (1.9%; 0.39/100 patient years) and malignancy rates (3.4%; 0.70/100 patient years) were comparable to previous publications on safety.

Conclusion
The present study showed an estimated 5-year sustained benefit of 55.7% in Crohn’s disease patients with infliximab maintenance therapy. Long-term use of infliximab was safe and reduced need for surgery in patients with scheduled maintenance therapy. Previous failure on infliximab should not absolutely preclude its future use in individual patients.
INTRODUCTION

Crohn’s disease (CD) is a chronic inflammatory disease affecting the entire gastrointestinal tract. The disease is clinically characterized by frequent relapses despite intensive medical and surgical therapy. These frequent relapses impair quality of life of CD patients and lead to high health care costs. The introduction of biological therapy some 15 years ago, targeting specific inflammatory cytokines, caused a revolutionary shift in the treatment options of CD. The first biological agent available for treatment of CD was infliximab (IFX), a monoclonal chimerical antibody directed against the inflammatory cytokine tumour necrosis factor-alpha (TNF). By supposedly neutralizing both membrane-bound and free TNF, CD-associated inflammatory activity is scaled down. The discovery of IFX therapy signified a major milestone in CD therapy since its success unlocked a new clue for a large set of new compounds targeting single proteins involved in the immune response.

In Europe, IFX is commercially available since 1999. In the years preceding approval, several large trials have shown its superiority compared to placebo in inducing and maintaining remission in luminal and fistulizing CD. However, a substantial number of patients is primary non-responder or develops antibodies against IFX that may lead to a loss of response or to adverse effects such as infusion reactions. Two factors that can reduce antibody formation – immunosuppressive co-medication and a scheduled treatment regimen rather than an ‘on demand’ strategy – appear to improve therapeutic efficacy. Still, however, IFX-therapy is not beneficial in all patients. Because of the chronic character of CD, usually debuting at young age, long-term effectiveness follow-up is of particular interest. However, few long-term data are available. Most clinical trials performed so far had a maximum follow-up of 12 months. Also, long-term data are pivotal to assess safety of therapy.

The randomized clinical trials that provided most of the current published efficacy data suffer from selection bias, which complicates translation of results into daily practice. Publications concerning daily practice data are scarce. The Academic Medical Centre (AMC) and the VU University Medical Centre (VUMC) are both high volume tertiary referral centres in Amsterdam, the Netherlands, with a comprehensive experience in anti-TNF therapy for inflammatory bowel disease (IBD). As a matter of fact, the first CD patient ever to receive IFX was treated at the AMC in 1992.

Aim of the present study was to add to the daily practice experience by presenting long-term effectiveness and safety results of 469 consecutive CD patients who received IFX to treat CD in the AMC or VUMC in the past decade.

PATIENTS AND METHODS

This retrospective cohort study concerned all consecutive CD patients since introduction of IFX who received the drug primarily to treat CD in the AMC or VUMC. In the AMC, the IBD database was searched digitally to identify all CD patients who were treated with IFX. All IBD patients from the VUMC were prospectively registered in an IFX database and CD patients were collected from this database.
Only CD patients with sufficient follow-up data to assess the end points were included in this analysis. The end of the study period was set on December 1st 2009 for AMC patients and April 1st 2010 for VUMC patients. If patients were referred to other hospitals or otherwise lost to follow-up, the date of the last contact with AMC or VUMC was considered the end of the follow-up period.

The Medical Ethical Committee of the AMC approved performance of this study.

All medical charts were retrospectively reviewed. Patient characteristics and circumstances at time of initiation of IFX-treatment were assessed. Treatment schedule was defined as ‘remission induction’ if a maximum of 3 infusions were administered within a period of 3 months. Subsequent maintenance therapy was defined as ‘episodic’ if IFX was given only upon relapse of symptoms or ‘scheduled’ if therapy was given following a regularly scheme.

End points
In this study, the following five end points were assessed:

1. Success rate of primary remission induction
Success rate was assessed by global physician’s assessment. Patients without sufficient response during the first three infusions were considered primary non-responders. Discontinuation of therapy within the first 3 infusions period because of an adverse event or comorbidity was also considered as failed remission induction.
Factors possibly affecting effectiveness were investigated by means of multivariate regression analyses. Factors investigated were the patient- and disease specific characteristics.

2. Sustained benefit of maintenance therapy
Failure-free survival of IFX treatment was measured in patients who after induction therapy were subsequently put on maintenance therapy.
Failure of maintenance therapy was defined as loss of response reported by global physician’s assessment or the occurrence of adverse events that led to discontinuation of IFX treatment. Discontinuation because of sustained remission, pregnancy or due to patients’ request did not qualify as treatment failure. These patients were censored at the time of discontinuation of IFX treatment. To determine the internal validity of the collected data and to rule out a hospital bias, the AMC- and VUMC-cohort were compared regarding the effectiveness outcome of maintenance therapy. Also of the maintenance phase, factors possibly affecting effectiveness were investigated.

3. Treatment success of retreatment with IFX
Retreatment with IFX was defined as a new IFX therapy episode after discontinuation of previous IFX therapy. Treatment success was similarly assessed as described in the primary episode. The outcome of retreated patients who previously had discontinued IFX treatment because of treatment failure was specifically addressed.
By means of univariate analysis assessed was whether additional therapies (resection, adalimumab therapy or trial medication) between the first and second IFX episode contributed to a favourable outcome of the second IFX treatment episode. Analyses were performed for the retreated patient group as a whole and for the sub group of patients who were retreated despite previous IFX failure.

4. Surgical interventions
The number of abdominal surgical interventions for complicated CD per 100 follow-up years before and after start of IFX were compared. A sub-analysis was performed for the group of patients who received scheduled maintenance therapy, irrespective of eventual treatment failure or success. In addition, timing of surgery after the first IFX administration was determined with stratification for IFX treatment success and failure. Abdominal surgical interventions consisted of resections, faecal diversion, stricture plasties and intra-abdominal abscess drainages.

5. Safety
An adverse event (AE) was defined as any reaction or side effect that occurred during the course of the treatment, whether or not the event was considered related to IFX therapy. Two categories were addressed in more detail: mortality and malignancy after initiation of IFX therapy. The relationship with IFX therapy was judged by three independent experts (PS, CP and AvB) in terms of not related, possibly related, probably related or certainly related to IFX therapy.

Statistical analysis
Continuous variables are presented as means with the standard deviation (SD). In case of skewed data, medians with the inter quartile range (IQR) are presented. For differences in proportions a chi-squared test or Fisher’s exact test was used. Univariate and multivariate regression analyses were performed to assess factors predictive for failure. Outcome hereof is presented as odds ratio (OR) with its 95% confidence interval (CI). The interval between start with IFX and moment of failure was determined by Kaplan-Meier analysis. From this analysis, the estimated 5-year benefit was calculated. The Kaplan Meier analysis was stratified for several factors. To test for a difference in failure-free survival, the log rank test was used. For comparison of the rates of abdominal surgical interventions pre- and post-IFX, the non-parametric bootstrap method was applied. With this method, samples of the same size as the original data set were drawn by sampling with replacement from the observed data. A bootstrap with 1000 replications was performed to obtain distribution of surgical rate differences. From these bootstrapped distributions the 95% CI and p-values were calculated. A Kaplan Meier analysis was performed to assess resection-free survival after start with IFX.
A p value of < 0.05 was considered statistically significant. Most statistical analysis was performed by using SPSS® software version 15.0 (SPSS Inc., Chicago, IL, USA). For the non-parametric bootstrap, statistical software from the R-project was used.
RESULTS

Since the introduction of IFX for CD in the studied centres, a total of 488 CD patients received IFX. From 19 patients, follow-up was insufficient to assess effectiveness. Of the remaining 469 (95.9%), 413 (84.6%) were still being treated at the two hospitals, whereas the other 55 were treated at other hospitals. Median follow-up was 4.5 years (IQR: 2.7 to 6.8) with a total of 2294 patient years. During the study period, a total of 8301 infusions were administered.

Patient characteristics are depicted in Table 1A and B; 1A shows general patient characteristics and 1B depicts the IFX-specific characteristics. Mean age at start of IFX was 33.3 years (SD: 12.1), after a median disease duration of 6.5 (IQR: 1.9 – 13.3) years.

1. Success rate of primary remission induction

Figure 1 shows the course of the primary IFX treatment episode of all patients who received IFX. The first subdivision in the algorithm shows that 70 patients (15%) had an unsuccessful remission induction course. Forty three patients had a primary non-response, 24 patients suffered from an adverse event and three patients had comorbidity irrespective of treatment success that required them to stop. This comorbidity consisted of dysplasia, a cardiovascular event and a bowel perforation each in one patient.

In univariate analysis, perforating CD behaviour ($p = 0.043$; OR: 1.860; 95% CI 1.020-3.392) and ‘no immunomodulating co-medication’ ($p = 0.001$; OR: 2.715; 95% CI 1.504-4.902) were found to be significantly associated with failure of remission induction. A resection in medical history showed a trend to an association with therapy success ($p = 0.070$; OR: 0.624; 95% CI 0.375-1.040). In multivariate analysis, adjusting for confounding factors, the only factor associated with unsuccessful remission induction remained ‘no immunomodulating co-medication’ ($p = 0.001$; OR: 2.757; 95% CI 1.506-5.044).

2. Sustained benefit of maintenance therapy

Of the 399 patients (85%) with successful remission induction, 316 patients continued with maintenance therapy (Figure 1). A successful scheduled maintenance course was noted in 169/276 (61%). In the episodic maintenance arm, 19/40 (48%) had a successful maintenance therapy. At 5 years, the overall estimated sustained benefit was 55.7% (95% CI: 48.8 – 62.6).

Maintenance therapy, either scheduled or episodic, was discontinued due to failure after a median treatment duration of 14.7 months (IQR 6.9 – 31.9) in 128 patients (40%). Of those, seven patients had comorbidity irrespective of (lack of) response that required them to stop. This comorbidity consisted of carcinoma or dysplasia in three, an infection in three and a cardiovascular event in one patient.

Table 2 clarifies timing and reason of discontinuation in all patients at risk during follow-up. No differences were found in the Kaplan Meier failure-free survival analyses stratified for AMC vs. VUMC ($p = 0.545$ for the entire cohort and $p = 0.743$ for the sub group of patients with maintenance therapy).
TABLE 1A: GENERAL PATIENT CHARACTERISTICS AND TABLE 1B: CHARACTERISTICS AT START OF IFX

**Table 1A: General patient characteristics**

<table>
<thead>
<tr>
<th>Total: n = 469</th>
<th>(% / SD / IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M / F</td>
<td>168 / 301</td>
</tr>
<tr>
<td>Montreal classification</td>
<td></td>
</tr>
<tr>
<td>Age (A1/A2/A3)</td>
<td>96 / 338 / 35</td>
</tr>
<tr>
<td>Location (L1/L2/L3/(also) L4)</td>
<td>114 / 154 / 195 / 66</td>
</tr>
<tr>
<td>Behavior (B1/B2/B3/also Bp)</td>
<td>230 / 118 / 121 / 207</td>
</tr>
<tr>
<td>Extra intestinal manifestations</td>
<td></td>
</tr>
<tr>
<td>Y / N (missing: 36)</td>
<td>231 / 202</td>
</tr>
<tr>
<td>- Arthralgia</td>
<td>188</td>
</tr>
<tr>
<td>- Cutaneous</td>
<td>49</td>
</tr>
<tr>
<td>- Uveitis/conjunctivitis</td>
<td>16</td>
</tr>
<tr>
<td>- Oral aphthous lesions</td>
<td>20</td>
</tr>
<tr>
<td>- Miscellaneous</td>
<td>1</td>
</tr>
<tr>
<td>Age at time of diagnosis*</td>
<td>24.47</td>
</tr>
<tr>
<td>Age at end of study period*</td>
<td>38.18</td>
</tr>
<tr>
<td>Operations before start IFX</td>
<td></td>
</tr>
<tr>
<td>Y: N</td>
<td>247 / 222</td>
</tr>
<tr>
<td>- intra-abdominal</td>
<td>137</td>
</tr>
<tr>
<td>- perianal</td>
<td>65</td>
</tr>
<tr>
<td>- both</td>
<td>54</td>
</tr>
<tr>
<td>Number of resections: 1/2/3/&gt;3</td>
<td>95/53/20/17</td>
</tr>
<tr>
<td>Number of perianal operations: 1/2/3/&gt;3</td>
<td>66/20/15/14</td>
</tr>
<tr>
<td>At least one resection before start IFX</td>
<td></td>
</tr>
<tr>
<td>Y:N</td>
<td>191 / 278</td>
</tr>
<tr>
<td>- right sided</td>
<td>107</td>
</tr>
<tr>
<td>- left sided</td>
<td>18</td>
</tr>
<tr>
<td>- both</td>
<td>53</td>
</tr>
<tr>
<td>- small bowel resection</td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 1B: Characteristics at start of IFX**

<table>
<thead>
<tr>
<th>Total: n = 469</th>
<th>(% / IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of start IFX (years)*</td>
<td>33.32</td>
</tr>
<tr>
<td>Disease duration at start IFX (years)†</td>
<td>6.45</td>
</tr>
<tr>
<td>CRP at time of start IFX (Missing: 102)†</td>
<td>15.3</td>
</tr>
<tr>
<td>Co-medication at time of start IFX</td>
<td></td>
</tr>
<tr>
<td>Y / N (missing: 18)</td>
<td>397 / 54</td>
</tr>
<tr>
<td>- AZA/6MP/6TG/MTX</td>
<td>373</td>
</tr>
<tr>
<td>- steroids</td>
<td>53</td>
</tr>
<tr>
<td>- 5-asa</td>
<td>14</td>
</tr>
<tr>
<td>Indication for IFX</td>
<td></td>
</tr>
<tr>
<td>Luminal</td>
<td>312</td>
</tr>
<tr>
<td>Fistulizing</td>
<td>93</td>
</tr>
<tr>
<td>Both luminal and fistulizing</td>
<td>51</td>
</tr>
<tr>
<td>Extra intestinal manifestations</td>
<td>13</td>
</tr>
<tr>
<td>Scheme of IFX medication</td>
<td></td>
</tr>
<tr>
<td>Remission induction only</td>
<td>153</td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>316</td>
</tr>
<tr>
<td>- Episodic</td>
<td>40</td>
</tr>
<tr>
<td>- Scheduled</td>
<td>276</td>
</tr>
</tbody>
</table>

* mean (SD); † median (IQR). Montreal classification: A: age at diagnosis (A1 <17; A2 17-40; A3 >40); L: location of disease activity (L1 ileocecal; L2 colonic; L3 both; L4 short bowel); B: behavior of disease (B1 inflammatory disease; B2 stricturing disease; B3 perforating disease; Bp: perianal disease)
FIGURE 1: COURSE OF PRIMARY IFX EPISODE

469 patients with IFX therapy

Unsuccessful remission induction: 70
- primary non response: 43
- adverse effects: 24
- co morbidity: 3

Successful remission induction: 399

Other / no therapy: 83

Maintenance therapy: 316

Scheduled maintenance therapy: 276

Unsuccessful scheduled therapy: 107
- adverse effects: 26
- loss of response: 74
- co morbidity: 7

Successful scheduled therapy: 169

Episodic start of maintenance therapy: 40

Unsuccessful episodic therapy: 21
- adverse effects: 6
- loss of response: 15

Successful episodic therapy: 19

Discontinuation of successful scheduled therapy: 43
- remission: 27
- pregnancy: 6
- patient’s request: 10
- co morbidity: 7

Still using IFX: 126

Still using IFX: 11
In univariate analysis, a diagnosis after the 40th year of life (Montreal classification A3) was significantly associated with failure of maintenance therapy ($p = 0.015; \text{OR: } 3.407; \text{95\% CI: } 1.274-9.112$). In multivariate analysis, no factors were found to be associated with failure.

Figure 2a and b show the failure-free survival of all patients who entered the maintenance therapy phase. The first curve represents the 316 patients; Figure 2b shows the data stratified for indication. In other stratification analyses, patients who received immunomodulating co-medication at start of IFX were found to experience

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**TABLE 2: FIRST IFX EPISODE: TIME AND REASON OF DISCONTINUATION IN ALL PATIENTS AT RISK DURING FOLLOW-UP**

<table>
<thead>
<tr>
<th>Number of pts. with IFX discontinuation</th>
<th>&lt; 3 months (N = 153)</th>
<th>3 months – 1 year (N = 84)</th>
<th>1 – 2 years (N = 66)</th>
<th>2 – 3 years (N = 42)</th>
<th>3 – 5 years (N = 66)</th>
<th>5 - 11 years (N = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
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</tr>
<tr>
<td>Response</td>
<td>83</td>
<td>31</td>
<td>36</td>
<td>26</td>
<td>51</td>
<td>44</td>
</tr>
<tr>
<td>- 77: remission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 2: pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- 4: pts’ request</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 11: still using IFX (but fu not longer)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>67</td>
<td>50</td>
<td>29</td>
<td>15</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>- 42: primary NR</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>- 24: AR</td>
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<tr>
<td>- 14: AR</td>
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<tr>
<td>- 21: LOR</td>
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<tr>
<td>- 8: AR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Patients at risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start: N = 469</td>
<td>Left at 3 months:</td>
<td>Left at 1 year:</td>
<td>Left at 2 years:</td>
<td>Left at 3 years:</td>
<td>Left at 5 years:</td>
<td>Left at 11 years:</td>
</tr>
<tr>
<td>=&gt; N = 316</td>
<td>=&gt; N = 232</td>
<td>=&gt; N = 166</td>
<td>=&gt; N = 124</td>
<td>=&gt; N = 58</td>
<td>=&gt; N = 58</td>
<td>N = 0</td>
</tr>
<tr>
<td>Co morbidity</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NR: non response; fu: follow-up; LOR: loss of response; AR: adverse reaction; pts’: patients’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR: non response; fu: follow-up; LOR: loss of response; AR: adverse reaction; pts’: patients’

In univariate analysis, a diagnosis after the 40th year of life (Montreal classification A3) was significantly associated with failure of maintenance therapy ($p = 0.015; \text{OR: } 3.407; \text{95\% CI: } 1.274-9.112$). In multivariate analysis, no factors were found to be associated with failure.

Figure 2a and b show the failure-free survival of all patients who entered the maintenance therapy phase. The first curve represents the 316 patients; Figure 2b shows the data stratified for indication. In other stratification analyses, patients who received immunomodulating co-medication at start of IFX were found to experience
significantly less failures and, if so, then later (p = 0.011). Furthermore, a diagnosis after 40 was again associated with worse outcome (p = 0.009). No differences were found for steroid use at start with IFX (p = 0.072), a resection prior to IFX therapy (p = 0.647), and scheduled versus episodic therapy (p = 0.288).

3. Treatment success of retreatment with IFX

Figure 3 depicts the course of treatment during the second episode of 131 patients who received a second episode of IFX therapy. Outcome was similar to the first episode with successful remission induction in 82% of patients and successful maintenance therapy in 65%. Fifty-seven patients were considered failure in their first treatment episode. The second treatment episode turned out to be clinically beneficial in 27 of these 57 patients (47%).

**FIGURE 3: COURSE OF SECOND IFX EPISODE**

- Successful first episode: 72
  - Unsuccessful first episode: 59
    - primary non response: 20
    - adverse effects: 17
    - loss of response: 20
    - co morbidity: 2

- Successful remission induction: 108

- Unsuccessful remission induction: 23
  - non response: 5
  - adverse effects: 18

- Other / no therapy: 13

- Maintenance therapy: 95
  - Unsuccessful maintenance therapy: 33
    - adverse effects: 8
    - loss of response: 22
    - co morbidity: 3

- Successful maintenance therapy: 62
  - Discontinuation of successful maintenance therapy: 21
    - remission: 18
    - patients' request: 2
    - pregnancy: 1

- Still using IFX: 41
Outcome of the second IFX episode was not influenced by a resection, adalimumab therapy or trial medication between the first and second IFX episode (data not shown).

4. Surgical interventions

Figure 4 shows the number of abdominal surgical interventions per 100 patient years before and after initiation of IFX-treatment. The decrease from 9.63 to 8.62 interventions per 100 patient years was not statistically different ($p = 0.356$).

In the subgroup of patients with scheduled maintenance therapy, a significant decrease in surgical intervention rates was observed after start with IFX. Before start with IFX this group of 276 patients underwent 8.76 abdominal surgeries per 100 patient years; after start this decreased to 6.06 interventions, a reduction of 31% (absolute reduction: 2.70; 95% CI: -4.82 to -0.35; $p = 0.018$). When dividing the cohort with scheduled maintenance therapy in groups with and without prior resection before IFX therapy, 27 of 112 patients with a prior resection required a reoperation after start with IFX (24%, predominantly right-sided surgery (n=17 (63%) or small bowel (n=6 (22%)). In the group of 164 patients with no resection prior to IFX, 30 patients required a resection after receiving IFX therapy (18%). Most of these patients underwent right-sided surgery (n=22; 73%). Therefore, no protective effect of prior resection was seen in the 112 patients with a resection before start with IFX therapy. In Kaplan Meier analysis of surgery-free survival after start of IFX therapy of the entire cohort, therapy success led to less and more postponed surgical interventions compared with therapy failure ($p < 0.001$).

**FIGURE 4: ABDOMINAL SURGERY PRE- AND POST-IFX PER 100 PATIENT YEARS**

![Bar chart showing abdominal surgeries pre- and post-IFX therapy](chart.png)

- **Abdominal surgery prior to IFX therapy**: 9.63 (Total cohort n=469)
- **Abdominal surgery after start with IFX**: 8.62
- **Abdominal surgery prior to IFX therapy**
- **Abdominal surgery after start with IFX**: 8.76 (Maintenance - scheduled n=276)
- **Maintenance - scheduled n=276**
- **$p = 0.356$**
- **$p = 0.018$**
5. Safety

Fifty-six patients (12%) discontinued the first IFX therapy episode due to adverse effects (Figure 1). An infusion reaction was reason of withdrawal in 32 patients (57%; 7% of whole cohort); five patients (9%) stopped due to onset or worsening of arthralgia; three patients (5%) had a lupus like syndrome, two patients (4%) had a delayed type hypersensitivity; cutaneous eruptions were seen in two (4%); general malaise was seen in two (4%); infection in three (5%); neurological symptoms in two (4%). Anaphylactic shock; oedema; abscess formation; headache and depressive symptoms were each documented in one patient (2%). Ten patients discontinued IFX therapy because of comorbidity.

The second episode of IFX therapy was discontinued in 26 patients (20%) due to adverse effects (Figure 3). This was a significantly higher proportion compared with the number of patients discontinuing the first IFX episode because of adverse effects (20% vs. 12%; p = 0.020). Of these 26 patients, five had also discontinued the first IFX episode because of adverse effects.

Mortality

Nine patients (1.9%; 0.39/100 patient years) died after a median number of 4 infusions (IQR: 2.0 - 6.5). Median time between last infusion and death was 6.5 months (IQR: 3.5 - 48.7), making it unlikely that this was directly related to IFX-therapy for most patients. The individual causes of death are listed in Table 3. Suspected association with IFX is indicated. Of one patient the exact cause of death remained unknown, for she died while being abroad for a second opinion in her nation of birth.

<table>
<thead>
<tr>
<th>TABLE 3: DEATHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
</tr>
</tbody>
</table>

| Age at time of death | 47.9 (40.5 – 53.7)* |
| Time after last IFX infusion (months) | 6.5 (3.5 – 48.7)* |
| No of infusions | 4.0 (2.0 – 6.5)* |

<table>
<thead>
<tr>
<th>Individual causes of death</th>
<th>Death: number of months after last IFX administration</th>
<th>No of IFX infusions received</th>
<th>Age at death</th>
<th>Relation estimated by experts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. EBV-related B-cell lymphoma</td>
<td>1.91</td>
<td>4</td>
<td>59.0</td>
<td>Possibly</td>
</tr>
<tr>
<td>2. Metastasized rectal cancer</td>
<td>6.12</td>
<td>29</td>
<td>57.4</td>
<td>Possibly</td>
</tr>
<tr>
<td>3. Metastasized lung carcinoma</td>
<td>73.12</td>
<td>1</td>
<td>44.5</td>
<td>Possibly</td>
</tr>
<tr>
<td>4. Jejunal carcinoma</td>
<td>5.16</td>
<td>6</td>
<td>40.5</td>
<td>Possibly</td>
</tr>
<tr>
<td>5. Rectal carcinoma</td>
<td>75.75</td>
<td>3</td>
<td>47.9</td>
<td>Possibly</td>
</tr>
<tr>
<td>6. Bilateral pneumonia</td>
<td>0.43</td>
<td>4</td>
<td>23.4</td>
<td>Probably</td>
</tr>
<tr>
<td>7. Bowel perforation</td>
<td>6.54</td>
<td>3</td>
<td>50.0</td>
<td>Possibly</td>
</tr>
<tr>
<td>8. Myocardial infarction</td>
<td>21.57</td>
<td>1</td>
<td>39.5</td>
<td>Possibly</td>
</tr>
<tr>
<td>9. Unknown (in clinic in Egypt)</td>
<td>8.21</td>
<td>5</td>
<td>42.9</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Total no of patients that died 9 (1.9%)

*median (IQR)
Malignancy

In total, 16 patients (3.4%; 0.70/100 patient years) developed a (pre)malignancy. These were gastrointestinal (n=6); haematological (n=3); respiratory (n=3), gynaecological (n=2) and skin (n=2) malignancies. In nine patients (median age 49 (IQR 42-56)) it was diagnosed during IFX therapy, after a median of 10 (IQR 3-22) infusions. In the remaining seven patients, IFX was discontinued for median 36 (IQR 8-57) months after 3 (IQR 1-12) infusions. Median age was 45 (IQR 37-46). All malignancies were estimated to be possibly related by to IFX by the experts. Five patients died due to malignancy, these are listed in Table 3 and discussed in the paragraph on mortality.

**DISCUSSION**

With a median follow-up of almost 4.5 year in 469 CD patients, the present study is one of the few large IFX cohorts presented to date. This study showed that remission induction with IFX was successful in 85% of patients. Sustained clinical benefit was estimated to amount to 55.7% at five years. Scheduled IFX therapy was associated with less need for surgery.

Compared to the large randomized trials that evaluated one-year efficacy, the global benefit of therapy appears favourable. In our cohort at 12 months, maintenance therapy was considered successful in approximately 80% (Figure 2a), whilst in the two randomized studies that were evaluated in the Cochrane review regarding anti-TNF as maintenance therapy, response was seen in 44%-62% and remission in 33% - 53% of patients \cite{17}. This difference can be explained by the applied criteria for response (a Crohn’s disease activity index (CDAI)-drop of > 70 points) and remission (CDAI < 150) that were used in these intervention trials. In daily practice, global physician’s assessment rather than changes in disease activity score is used to decide whether a patient has a favourable response or not. The present study reflects this daily practice.

Few data on long-term daily practice outcome of IFX outcome (>1 year) are available. Only one large single centre cohort similar to the present study has been published, by Schnitzler et al. \cite{18}. In this Belgian cohort, a sustained benefit of 63.4% in patients receiving maintenance therapy was reported. In their series, sustained benefit was defined as lasting control of disease during follow-up. The corresponding figure in our cohort was 61%. This approach does not account for the length of the period the patient had benefit of the treatment. Hence, a patient who has 4 years of therapy benefit before he develops an adverse reaction in the end will be counted as a failure, while in daily clinical practise this would hardly be qualified as such. In our cohort 13 patients developed a failure after 5 to 11 years of IFX treatment. Conversely, 11 patients were regarded as treatment success while having a follow up time of only 3 months to one year. It is conceivable that some of these patients would qualify as failures if follow-up time had been longer. Therefore, we feel that the most proper way of describing the long-term results of IFX therapy is by Kaplan-Meier survival estimates.

Also, Schnitzler et al. reported a significantly higher proportion of patients needing major abdominal surgery in those who were primary non-responders. Since IFX is indicated for therapy refractory disease it is obvious that for primary non-responders, surgery is imminent in many cases. Therefore, in order to assess the protective effect of IFX treatment on future surgery, we judged it more appropriate to analyse only patients who (a) received an optimal treatment regimen (a scheduled maintenance therapy regimen) \cite{19}, and (b) had the right indication...
for IFX therapy (the fact that these patients received maintenance therapy suggests that induction therapy was successful, which means that fibrotic patients who should have undergone surgery on beforehand were filtered out).

CD is a progressive disease in which longer disease duration comes with a higher risk of having to undergo surgery. The finding that the rate of abdominal surgery in patients on scheduled maintenance therapy was significantly reduced after start with IFX in our cohort, corroborates with the hypothesis that IFX shows promise as preventive therapy for future Crohn’s related surgery. This is in conflict with publications suggesting that IFX only postpones rather than prevents surgery. It must be noted that the reduction of surgery found in this study concerns a selected group of patients. Patients with too severe CD activity to respond to IFX and patients with fibrotic CD were excluded. In the total cohort, no reduction was found, which is in accordance with the literature. Furthermore, in this rough retrospective analysis, no correction for confounders could be performed. A prior resection seemed however not to be protective for later surgery.

Several other studies on IFX effectiveness in daily practice were published, but these were limited by rather small cohorts and a limited period of follow-up.

In contrast to the data from the Leuven group, we observed a correlation between the combination of IFX with immunomodulatory drugs and a favourable therapeutic outcome. This is in concordance with the recently published results from the SONIC-trial.

An additional factor that impaired favourable response to IFX therapy was a higher age at diagnosis. To our knowledge, this association has not been reported in literature and it may either be the result of a type 1 error or a consequence of the fact that the Montreal age classification truly reflects a distinct type of CD that responds less well to anti-TNF treatment.

In this study a similar rate of successful therapy was noted in patients retreated with IFX in a second episode. Remarkably, previous failure was not predictive for failure in later episodes, for 47% of the 57 patients who failed on their first IFX episode and subsequently received a second course, did experience clinical benefit from this second course. Some of the first-episode failures might be explained by an improper indication, such as fibrotic-type disease needing surgical repair instead of medical therapy. Moreover, therapeutic response might have been awaited too impatiently in some patients. It is unlikely that this accounts for all unsuccessful first episodes. Retreatment with IFX in patients previously failing on IFX may thus be worthwhile in the setting of disease refractory to other treatment modalities. A resection, trial medication or adalimumab between the first and second IFX episode did not influence outcome of the second IFX therapy.

Mortality was 1.9%, or 0.39/100 patient years in these series. This outcome is comparable to the rate of 0.3/100 patient years documented by Fidder et al., and the 0.53/100 patient years reported from the TREAT registry. The single case of bilateral pneumonia in these series was considered ‘probably related’ to IFX; all other known causes of death were judged to be possibly related to IFX.

(Pre-)malignancies were found in 3.4% of patients, that is 0.70/100 patient years, with higher incidences in patients aged 40-70 as compared to patients aged 10-40. This was higher compared to the 0.4/100 patient years malignancy rate found by Fidder et al. If excluding the three pre-malignant cases, the rate of 0.57/100 patient years
years was still higher but the absolute percentage was comparable to other long-term studies evaluating the risk of cancer in anti-TNF therapy in IBD. It is complicated to assess the degree of IFX involvement in the pathogenesis of neoplasia in the course of IBD. Considering the pleiotropic effects of TNF, IFX cannot be ruled out to be related with development of any neoplasia. Most patients, however, usually have immunosuppressive (co-) medication also alleged to contribute to neoplasia generation. Therefore, it remains a matter of discussion. Overall, the absolute risk seems to be rather limited.

In comparison to literature, the rate of serious infections leading to discontinuation was low. More infections have occurred in this series, however without any consequence for continuation of therapy. Nevertheless, the true infection rate may possibly have been higher and under-reported in the IBD charts. An intrinsic shortcoming of this study is its retrospective nature. This may have affected assessment of both effectiveness as well as adverse events. Considering the retrospective design, disease activity scales were not measured regularly and not all patient data could be retrieved. Global physicians’ assessment however correlates rather well with CDAI. With regard to adverse events, full documentation was lacking, and under-reporting cannot be ruled out. In case of infusion reactions, these were only consistently documented when they were severe and if they led to discontinuation of therapy. On the other hand, the series from the AMC and the VUMC separately showed similar numbers of therapeutic response and adverse events. This consistency indicated that hospital records were reliable, as similar administrative inaccuracy at two sites is unlikely.

In conclusion, the present study showed that long-term real life treatment with IFX for CD has long-standing sustained benefit in more than half of patients. Long-term use of IFX is safe and prevents surgery in a selected cohort of patients on scheduled maintenance therapy. Previous therapeutic failure on IFX should not absolutely preclude its future use in individual patients.
Reference List


