Optimizing anti-TNF therapy in inflammatory bowel disease
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CHAPTER 9

Effects of infliximab retreatment after consecutive discontinuation of infliximab and adalimumab in refractory Crohn’s disease


ABSTRACT

Background and aim
Switches between anti-TNF agents in the treatment of Crohn’s disease (CD) occur in case of treatment failure, intolerance or patient preference. No data are currently available on the usefulness of a second infliximab treatment after earlier discontinuation and previous switch to an alternative anti-TNF agent. In the current study we evaluated the clinical benefit of infliximab retreatment in CD patients after sequential use of both infliximab and adalimumab.

Methods
Twenty-nine CD patients who had received earlier treatments with sequential infliximab and adalimumab and were then restarted on infliximab were retrieved from a multicenter registry designed for the follow-up of adalimumab treatment for CD. Short-term and sustained effects of infliximab retreatment were evaluated retrospectively by reviewing clinical records. Follow-up was 18 months for all patients.

Results
In 13/29 (45%) patients, Infliximab was re-introduced at intensified dosing schedule (>5mg/kg or <8 weeks), for 23/29 (79%) of patients similar to the schedule they were on at time of previous discontinuation. During the second infliximab treatment course, dosing was further intensified in 11 out of 29 (38%) patients. After 18 months 18/29 (62%) patients were still on continued therapy of their second infliximab treatment. Infliximab was discontinued (after a median of 7 months) in 11 out of 29 patients for loss of response (n=7, 24%), intolerance (n=3, 10%) or non-compliance (n=1, 3%).

Use of induction schedule or concomitant immunomodulators were not significantly associated with treatment benefit.

Conclusions
The majority of CD patients benefit from a second treatment with infliximab after previous treatment with infliximab and adalimumab, which offer a meaningful therapeutic option in often highly refractory patients.
Introduction

In the past decades several biological drugs that target Tumor Necrosis Factor (TNF) have improved the management and outcome of Crohn’s disease (CD) patients. Infliximab (IFX), a chimeric (mouse/human) anti-TNF monoclonal antibody, has demonstrated its efficacy for induction and maintenance therapy in moderate to severe luminal and fistulizing CD.\textsuperscript{1-3} Moreover, combination therapy with IFX and azathioprine proved to be superior in increasing the likelihood of corticosteroid-free clinical remission in CD patients compared to IFX and azathioprine monotherapy.\textsuperscript{4} Adalimumab (ADA) represents the second anti-TNF antibody that became available for the treatment of refractory CD. ADA proved to be superior to placebo in inducing clinical response, clinical remission and mucosal healing in refractory CD.\textsuperscript{5-8}

Despite this important progress in treatment options, primary non-response to anti-TNF therapy has been reported in roughly one third of CD patients.\textsuperscript{1,4,5} Furthermore, in patients who initially respond to anti-TNF therapy, a significant proportion of patients lose their response over time.\textsuperscript{9-12} Various mechanisms explaining this phenomenon of ‘secondary’ loss of response include formation of neutralizing antibodies directed against the therapeutic antibodies, low serum drug concentrations, abundance of TNF to be neutralized (high inflammatory load) and other causes of antibody degradation.\textsuperscript{12-14}

In clinical practice a considerable proportion of CD patients are switched from one anti-TNF agent to the other for loss of response, intolerance or patient preference. However, anti-TNF naive patients usually have higher response rates than patients who have previously been exposed to other TNF agents.\textsuperscript{5,10,11} Since anti-TNF agents are costly therapies that are often considered the last resort before surgery, it is important to evaluate the outcome of a switch between different TNF blockers.

After loss of response to the regular doses of IFX (5 mg/kg every 8 weeks), dose escalation is the most common strategy offered to these patients. It has been shown this approach yields more quality-adjusted-life years compared to switching to ADA, however at a considerably higher cost.\textsuperscript{15}

A switch from IFX to ADA was shown to be effective in inducing and maintaining remission in CD patients who lost their response or became intolerant to IFX.\textsuperscript{16-22} A systematic assessment of patients’ preference when choosing an anti-TNF agent revealed preference for subcutaneous administration.\textsuperscript{23} Nonetheless, the randomized SWITCH trial showed that elective switching from IFX to ADA leads to a considerable risk of relapse and therefore should not be routinely recommended.\textsuperscript{24, 25}

IFX was registered for use in CD many years earlier than ADA (1998 vs. 2007). As a consequence, many CD patients received initial treatment with IFX and then, for a variety of reasons, switched to ADA. In case of failure to ADA treatment, the question comes up
whether retreatment with IFX could be a feasible option. Currently, there are no data available regarding the long term effects of retreatment with IFX in patients who have sequentially failed IFX and ADA. An open label French study looked at the benefit of introducing a third anti-TNF agent (CZP) and showed benefit in 45% of patients up to 9 months.26, 27

This retrospective study aimed to evaluate the clinical benefit of IFX retreatment in CD patients who had sequentially used and discontinued IFX and ADA.
Materials and Methods

Study population

CD patients from North-Holland who were treated with ADA between November, 2003 and November 2010 were identified through 'Zorgapotheek', the sole distributor of ADA in the Netherlands. These patients were included in an observational cohort study evaluating clinical outcomes and safety with ADA for CD. Eighteen hospitals participated in the cohort study, including two tertiary referral centres and sixteen regional hospitals belonging to the North Holland Gut Club.

From this cohort of 438 CD patients treated with ADA for at least 3 months, we identified those who had previously been treated with IFX for at least 3 months and received a second IFX treatment after ADA discontinuation. (Figure 1) Twenty nine patients fulfilled these criteria and in all of these follow-up was available for at least 18 months.

Figure 1 Flow chart of inclusion

Data collection

We reviewed patient records for demographics, medical history, Montreal classification, and treatments, IFX dosing, and dose escalation and reasons for discontinuation of anti-TNF treatment, concomitant immunosuppression, clinical response, adverse events and duration of follow-up. Where available, ADA and IFX antibody levels were recorded. The number of surgical interventions before and after the second IFX start was recorded. Global Physician Assessment was monitored at baseline, at the start of the second IFX treatment (IFX2) and then within quartiles during the first 12 months and again at 18 months follow-up.
Endpoints

The primary endpoint of this study was sustained clinical benefit of IFX retreatment defined as ongoing maintenance treatment with this agent without major bowel surgery (bowel resection), but irrespective of therapy intensification. Patients in ‘clinical remission’ and/or ‘clinical response’ at all visits were considered to have ‘sustained clinical benefit’, which is presented as failure-free survival upon follow-up.

‘Clinical remission’ was defined as absence of CD-related symptoms including diarrhea, abdominal pain and drainage of fistulas (or Harvey Bradshaw Index <4).31 ‘Clinical response’ was defined as persisting although reduced severity of diarrhea and abdominal pain and/or reduction of fistula drainage, when present/applicable (or Harvey Bradshaw Index 4-7). Symptoms were retrieved for the electronic medical records where these are systematically collected. ‘Discontinuation of treatment’ was defined as a permanent stop of IFX therapy. Failure was defined as cessation of IFX therapy due to non-response within the first 3 months of reintroduction (remission induction phase), loss of response after successful remission induction or adverse events necessitating treatment discontinuation. Major bowel surgery (bowel resection) was also considered failure of therapy, whereas adhesiolysis or seton drainage of pre-existing fistula (prior to IFX retreatment) were not.

Patient, disease and treatment specific factors were tested for possible association with failure-free survival. A secondary endpoint was safety of IFX reintroduction. An adverse event was defined as any reaction that occurred since the start of treatment, being related to IFX by the treating physician. Adverse events were classified according to WHO guidelines.32, 33 Concomitant immunomodulatory treatment was defined as the use of either thiopurines (azathioprine, 6-mercaptopurine, 6-thioguanine) or methotrexate in the first 3 months of (re-)initiation of anti-TNF therapy. Therapy intensification was considered either dose increase or interval decrease.

Statistical analysis

We used descriptive statistics in percentages with 95% confidence intervals for discrete variables or means with standard deviations (SD). Skewed data were presented as median with interquartile range (IQR). For differences in proportions a Fisher’s exact test was used. The interval between start of treatment and time point of failure was estimated by Kaplan-Meier analysis of failure-free survival. A p<0.05 was considered statistically significant. SPSS® software version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Ethical approval was obtained in all participating hospitals for reviewing medical records for the total CD cohort treated with ADA.
Results

Baseline Patient characteristics (Table 1.)

A total of 29 CD patients (female 76%) from 8 hospitals, who were re-started on IFX therapy after previous consecutive use of IFX and ADA were identified. At IFX re-introduction (IFX2), their median age was 31 (IQR 26-40) years and the median disease duration amounted to 8.0 years (IQR 7-13). Approximately half of the (52%) patients had ileocolonic CD according to the Montreal classification. Forty-eight percent of patients had penetrating disease, while 21% was classified as stricturing and 31% as non-stricturing and non-penetrating disease. Peri-anal disease was present in 18 out of 29 patients (62%), whereas extra-intestinal manifestations had been recorded in one third (34%) of patients. Twenty-one patients (72%) had undergone CD-related surgical intervention prior to retreatment with IFX, of which ileocecal resection was the most common (14/29, 41%).

Table 1. Baseline Patient Characteristics (n=29)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Female, n (%)</td>
<td>22</td>
</tr>
<tr>
<td>Age at start IFX2 (years), median (IQR)</td>
<td>31</td>
</tr>
<tr>
<td>Smoking: Current</td>
<td>6</td>
</tr>
<tr>
<td>Smoking: Never</td>
<td>15</td>
</tr>
<tr>
<td>Smoking: Former (stopped &gt;6mths)</td>
<td>3</td>
</tr>
<tr>
<td>Smoking: Unknown</td>
<td>5</td>
</tr>
<tr>
<td>Disease duration (years), median (IQR)</td>
<td>8</td>
</tr>
<tr>
<td>Age (years) at diagnosis Montreal classification: n (%)</td>
<td></td>
</tr>
<tr>
<td>A1 (&lt;16)</td>
<td>5</td>
</tr>
<tr>
<td>A2 (17-40)</td>
<td>23</td>
</tr>
<tr>
<td>A3 (&gt;40)</td>
<td>1</td>
</tr>
<tr>
<td>Disease location Montreal classification: n (%)</td>
<td></td>
</tr>
<tr>
<td>L1 (ileal)</td>
<td>5</td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>9</td>
</tr>
<tr>
<td>L3 (ileocolonic)</td>
<td>15</td>
</tr>
<tr>
<td>L4 (upper GI disease)</td>
<td>2</td>
</tr>
<tr>
<td>Disease behaviour Montreal classification: n (%)</td>
<td></td>
</tr>
<tr>
<td>B1 (non-stricturing, non-penetrating)</td>
<td>9</td>
</tr>
<tr>
<td>B2 (stricturing)</td>
<td>6</td>
</tr>
<tr>
<td>B3 (penetrating)</td>
<td>14</td>
</tr>
<tr>
<td>Peri-anal disease, n (%)</td>
<td>18</td>
</tr>
<tr>
<td>Extra-intestinal manifestations: n (%)</td>
<td></td>
</tr>
<tr>
<td>Arthropathy (IBD related)</td>
<td>10</td>
</tr>
<tr>
<td>Erythema Nodosum</td>
<td>7</td>
</tr>
<tr>
<td>Pyoderma Gangrenosum</td>
<td>1</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1</td>
</tr>
<tr>
<td>Surgical interventions for CD: n (%)</td>
<td>21</td>
</tr>
<tr>
<td>Ileocecal Resection</td>
<td>14</td>
</tr>
<tr>
<td>Small Bowel resection</td>
<td>2</td>
</tr>
<tr>
<td>Colonic resection</td>
<td>4</td>
</tr>
<tr>
<td>Temporary ileostomy</td>
<td>2</td>
</tr>
<tr>
<td>Peri-anal fistula/abscess drainage</td>
<td>4</td>
</tr>
<tr>
<td>Strictureplasty/Balloon Dilatation</td>
<td>1</td>
</tr>
</tbody>
</table>

Legends: IFX2, infliximab retreatment; GI, gastro-intestinal; IBD, inflammatory bowel disease; CD, Crohn's disease.
Previous anti-TNF Treatment prior to Infliximab Retreatment (Table 2.)

The median duration of the first IFX treatment was 44 months (IQR 14-69). Sixty-nine percent of the patients had used concomitant immunomodulators during that first IFX course (IFX1). In the first treatment IFX treatment course, anti-drug antibodies to IFX were discovered in 1/13 patients in whom the test was performed. The first IFX treatment course was intensified by dose increase or interval reduction in 13/29 (45%) patients. The reasons for discontinuation of IFX1 were loss of clinical response (55%), clinical remission (24%), patients’ preference to switch to subcutaneous treatment with ADA (10%) or intolerance to IFX (2 patients (7%) had an adverse event, due to delayed hypersensitivity reactions, for which IFX was discontinued). In two thirds of patients (66%) only one month had elapsed between discontinuation of the first IFX course and start of ADA.

| Table 2. Previous Anti-TNF treatment (n=29) | 1st IFX course | ADA course |
| Duration (months), median (IQR) | 44 (14-69) | 5 (3-11) |
| Concomitant immunomodulators: n (%) | 20 (69%) | 13 (45%) |
| Azathioprine | 13 (45%) | 8 (28%) |
| 6-Mercaptopurine | 1 (3%) | 1 (3%) |
| Methotrexate | 6 (21%) | 4 (14%) |
| Therapy intensification | 13 (45%) | 10 (35%) |
| Reason for stop/switch anti-TNF: n (%) | | |
| Remission | 7 (24%) | 0 |
| Primary Failure | 0 | 7 (24%) |
| Loss of response | 16 (55%) | 14 (48%) |
| Intolerance | 2 (7%) | 6 (21%) |
| Patient’s preference (route of administration) | 3 (10%) | 2 (7%) |
| Unknown | 1 (3%) | 0 |
| Adverse events: n (%) | | |
| Allergic reaction: delayed hypersensitivity | 2 (7%) | 1 (3%) |
| Allergic reaction: acute infusion reaction | 0 | 1 (3%) |
| Injection side reaction | 0 | 3 (10%) |
| Infecion | 0 | 1 (3%) |
| Antibodies Positive (>12 AU): n (%) | | |
| Negative | 12 (41%) | 13 (45%) |
| Unknown | 16 (55%) | 15 (52%) |
| Interval ≤ 1 month between stop and start IFX, n (%) | 19 (65%) | - |
| Interval ≤ 1 month between stop ADA and start IFX, n (%) | - | 19 (65%) |
| Interval (months) between stop and start 1st and 2nd IFX, median (IQR) | 14 (7-21) |

**Legends:** IFX, infliximab; ADA, Adalimumab; AU, arbitrary units.

ADA was used for a median of 5 months (IQR 3-11). During ADA treatment, 45% of the patients were using concomitant immunosuppressive drugs. Adverse events occurred in 21% of patients: most commonly injection site reactions (n=3, 10%), 1 ‘acute’ injection reaction (n=1, 3%), 1 delayed hypersensitivity reaction (n=1, 3%) and 1 infection (herpes keratitis) (n=1, 3%). Anti-drug antibodies to ADA were detected in 1/14 patient in whom the test was performed. Interval reduction of ADA from every other week to every week was done in 35% of patients. The reasons for ADA discontinuation were loss of response (48%), primary failure on ADA (24%), intolerance (21%) and elective switch back to IFX because
patient's preference for the intravenous route of administration (7%). Again two thirds of patients (66%) switched between ADA and reintroduction of IFX therapy within one month.

**Treatment Characteristics of Infliximab Retreatment (IFX2) (Table 3.)**

IFX was reintroduced for luminal disease activity in 62% of CD patients, combined luminal and fistulizing activity in 31% and fistulizing disease alone in 7% of the cases. A re-induction schedule at week 0.2 and 6 was initiated in 18 (62%) patients. Two patients developed an anaphylactic reaction to the 2nd and 3rd infusion, respectively, and did not receive further IFX treatment. IFX was reintroduced at same dose as at discontinuation of IFX1 in 23/29 (79%) of patients at induction. 3 patients started at lower dose and 3 at higher dose compared to the last dose at discontinuation of the first IFX course. IFX was restarted at an intensified initial maintenance schedule (with a dose of more than 5mg/kg body weight or a treatment interval < 8 weeks) in 13/29 (45%). IFX was re-started at 5 mg/kg in 20/29 (69%), 7.5 mg/kg in 1 patient and at 10 mg/kg in 8/29 (28%). The initial treatment interval of maintenance therapy varied from 4 weeks (n=1, 3%) to 8 weeks in 17 out of 29 (59%) patients.

**Table 3. Treatment Characteristics 2nd IFX course (n=29)**

| Referral hospital, n (%) | 17 (59%) |
| Indication IFX2: n (%) | 18 (62%) |
| Luminal | 2 (7%) |
| Fistulizing | 9 (31%) |
| CRP baseline (mg/L), median (IQR) | 9.5 (2-21) |
| Induction schedule, n (%) | 16 (55%) |
| No | 11 (38%) |
| Did not proceed after induction | 2 (7%) |
| Pre-treatment corticosteroids, n (%) | 11 (38%) |
| Prednisolon i.v. | 3 (10%) |
| Oral corticosteroids | 5 (17%) |
| Entocort | 7 (24%) |
| Azathioprine | 8 (28%) |
| 6-Mercaptopurine | 4 (14%) |
| Methotrexate | 8 (28%) |
| IFX2 dosage, n (%) | 20 (69%) |
| 5 mg/kg | 1 (3%) |
| 7.5 mg/kg | 8 (28%) |
| IFX2 maintenance frequency, n (%) | 17 (59%) |
| 4 weeks | 1 (3%) |
| 6 weeks | 8 (28%) |
| 7 weeks | 1 (3%) |
| 8 weeks | 2 (7%) |
| Did not proceed after induction | 13 (45%) |
| Intensified maintenance at re-introduction (>5mg/kg/<8 weeks), n (%) |

*Legends: IFX2, infliximab retreatment.*
Seventeen (59%) patients received pre-treatment with steroids accompanied by antihistamine agents. Immunomodulators were concomitantly used in 69% of patients. During the second IFX course, 11 of 29 (38%) patients underwent further therapy intensification after a median of 6 months (3-11), however in 4/11 of these patients IFX therapy was reduced again after 18 months.

**Sustained Clinical Benefit of Retreatment of IFX (IFX2)**

Sustained clinical benefit of IFX retreatment was observed in 93%, 83%, 79% and 72% of patients at 3, 6, 9 and 12 months of follow-up, respectively. (Figure 2, Figure 3) At the end of 18 months of follow-up 62% of patients had a sustained clinical benefit. Of those, 9 (31%) patients were in genuine clinical remission and 9 (31%) had clinical response while on continued treatment. Discontinuation of the second IFX therapy after 18 months follow-up in 9 patients (31%) was due to loss of response (n=7, 24%) (after 3, 5, 5, 7, 9, 17, 17 months, respectively), intolerance (n=3, 10%) (after respectively 1,2,10 months of which 2 acute infusion reactions during re-induction) and non-compliance, because of pre-existing psychosis (n=1, 3%).

![Clinical Outcome Retreatment with Infliximab](image)

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Discontinuation of therapy</th>
<th>Sustained clinical benefit</th>
<th>Clinical response</th>
<th>Clinical remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>2 (7%)</td>
<td>27 (93%)</td>
<td>19 (65%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>3-6</td>
<td>5 (17%)</td>
<td>24 (83%)</td>
<td>11 (38%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>6-9</td>
<td>6 (21%)</td>
<td>23 (79%)</td>
<td>10 (35%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>9-12</td>
<td>8 (28%)</td>
<td>21 (72%)</td>
<td>10 (35%)</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>12-18</td>
<td>11 (38%)</td>
<td>18 (62%)</td>
<td>9 (31%)</td>
<td>9 (31%)</td>
</tr>
</tbody>
</table>

**Figure 2** Clinical outcome of retreatment with infliximab
Seventeen (59%) patients received pre-treatment with steroids accompanied by antihistamine agents. Immunomodulators were concomitantly used in 69% of patients. During the second IFX course, 11 of 29 (38%) patients underwent further therapy intensification after a median of 6 months (3-11), however in 4/11 of these patients IFX therapy was reduced again after 18 months.

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**Table 4. Outcome Retreatment IFX after 18 months (n=29)**

<table>
<thead>
<tr>
<th>Further therapy intensification (dose/frequency), n (%)</th>
<th>11 (35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events, n (%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Allergic reaction: acute infusion reaction</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Allergic reaction: delayed hypersensitivity</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Antibodies positive (&gt;12 AU), n (%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Negative</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>16 (56%)</td>
</tr>
<tr>
<td>CRP after 12-18 months (g/dL), median (IQR)</td>
<td>10, 3 (2-22)</td>
</tr>
<tr>
<td>Endoscopic Remission, n (%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>No</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>Surgical intervention for CD, n (%)</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Ileocecal Resection</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Peri-anal fistula drainage</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Explorative laparotomy due to adhesion</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Draining Fistula during IFX2, n (%)</td>
<td>8 (28%)</td>
</tr>
</tbody>
</table>

**Legends:** IFX2, infliximab retreatment; AU, arbitrary units.

Twenty-eight percent (n=8) of patients had draining fistulas during the second course of IFX, which recurred after a median time of 5.5 months (IQR:2.5-10.5) after re-introduction of IFX. Of all patients, 7 (24%) patients underwent a Crohn’s disease related surgical intervention during the second IFX course, after a median of 5 months (IQR:3-8): 3 patients underwent an ileocecal resection (10%) (after 4, 8 and 12 months), 3 patients underwent...
surgical drainage because of peri-anal fistulas (10%) and 1 patient had an explorative laparotomy for adhesiolysis (3%). Two out of 3 patients who underwent ileocecal resection were continued with IFX post-operatively, one of them was still using IFX at 18 months (nevertheless both were considered failures).

None of the patient, disease or treatment specific factors that we examined were significantly associated with sustained clinical benefit. (Table 5.) A slight trend was observed with 6/7 (86%) patients, who discontinued ADA due to primary failure, achieving sustained clinical benefit compared to 12/22 (55%) of patients who discontinued ADA for other reasons. However, non-stricturing/non penetrating disease (Montreal B1) was significantly associated with a higher rate of clinical remission compared to a stricturing or penetrating disease course (6/9; 67% vs. 3/20; 15%, p=0.01, OR:11).

Patients who were in clinical remission at the end of the first IFX course before switching to ADA had a similar rate of sustained clinical benefit (4/7=57%) and clinical remission (2/7=29%) during the second IFX treatment course compared to patients who were not in clinical remission after the first IFX course (sustained clinical benefit: 13/21; 71%, clinical remission: 6/21; 29%). There was a trend suggesting that patients who were re-treated with IFX within 1 month after ADA discontinuation, were more likely to achieve clinical remission compared to those with longer than one month anti-TNF free intervals (8/19; 42% vs. 1/10; 10%, p=0.11, OR:6.55). Patients with a baseline C-reactive protein (CRP) ≤ 10 mg/L at re-introduction of IFX: had a higher rate of clinical remission (8/17, 47%) at 18 months than patients with baseline CRP >10 mg/L (p=0.02, OR:9.78).

Re-induction, pre-treatment with corticosteroids, concomitant use of immunomodulators or intensified maintenance schedule (IFX dose > 5mg/kg or treatment interval < 8 weeks) did not appear to be significantly associated with clinical remission or sustained clinical benefit rate of IFX retreatment in this cohort.

**Safety**

Upon retreatment with IFX, adverse events occurred in 3/29 patients (10%): 2 patients had an acute infusion reaction (one patient on co-immunomodulatory treatment) and 1 patient developed a delayed hypersensitivity reaction after 10 months (despite pre-treatment with steroids before IFX infusion). (Table 4.)

Anti-drug antibodies to IFX were measured in 45% of patients and were positive in both patients who developed an acute infusion reaction. The sole patient with positive antibodies (86 AU/mL) to IFX during the first treatment episode was in clinical remission 18 months after IFX was re-introduced. In contrast, the only patient with detectable antibodies against ADA, who previously had a delayed hypersensitivity reaction to IFX1, also developed an acute infusion reaction (with positive antibodies) and failure to IFX retreatment.

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surgical drainage because of peri-anal fistulas (10%) and 1 patient had an explorative laparotomy for adhesiolysis (3%).

Two out of 3 patients who underwent ileocecal resection were continued with IFX post-operatively, one of them was still using IFX at 18 months (nevertheless both were considered failures).

None of the patient, disease or treatment specific factors that we examined were significantly associated with sustained clinical benefit.

A slight trend was observed with 6/7 (86%) patients, who discontinued ADA due to primary failure, achieving sustained clinical benefit compared to 12/22 (55%) of patients who discontinued ADA for other reasons.

However, non-stricturing/non penetrating disease (Montreal B1) was significantly associated with a higher rate of clinical remission compared to a stricturing or penetrating disease course (6/9; 67% vs. 3/20; 15%, p=0.01, OR:11).

Patients who were in clinical remission at the end of the first IFX course before switching to ADA had a similar rate of sustained clinical benefit (4/7=57%) and clinical remission (2/7=29%) during the second IFX treatment course compared to patients who were not in clinical remission after the first IFX course (sustained clinical benefit: 13/21; 71%, clinical remission: 6/21; 29%).

There was a trend suggesting that patients who were re-treated with IFX within 1 month after ADA discontinuation, were more likely to achieve clinical remission compared to those with longer than one month anti-TNF free intervals (8/19; 42% vs. 1/10; 10%, p=0.11, OR:6.55).

Patients with a baseline C-reactive protein (CRP) ≤10 mg/L at reintroduction of IFX: had a higher rate of clinical remission (8/17, 47%) at 18 months than patients with baseline CRP >10 mg/L (p=0.02, OR:9.78).

Re-induction, pretreatment with corticosteroids, concomitant use of immunomodulators or intensified maintenance schedule (IFX dose > 5mg/kg or treatment interval < 8 weeks) did not appear to be significantly associated with clinical remission or sustained clinical benefit rate of IFX retreatment in this cohort.

Safety

Upon retreatment with IFX, adverse events occurred in 3/29 patients (10%): 2 patients had an acute infusion reaction (one patient on concomitant immunomodulatory treatment) and 1 patient developed a delayed hypersensitivity reaction after 10 months (despite pretreatment with steroids before IFX infusion).

Anti-drug antibodies to IFX were measured in 45% of patients and were positive in both patients who developed an acute infusion reaction. The sole patient with positive antibodies (86 AU/mL) to IFX during the first treatment episode was in clinical remission 18 months after IFX was reintroduced. In contrast, the only patient with detectable antibodies against ADA, who previously had a delayed hypersensitivity reaction to IFX1, also developed an acute infusion reaction (with positive antibodies) and failure to IFX retreatment.

**Table 5. Factors associated with clinical outcome**

<table>
<thead>
<tr>
<th>Factors associated with clinical outcome</th>
<th>Sustained clinical benefit</th>
<th>Clinical remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline patient characteristics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Montreal Behaviour (B1 vs. other)</td>
<td>67% vs. 50% (ns)</td>
<td>67% vs. 15% (p=0.01, OR:11)</td>
</tr>
<tr>
<td>- Previous surgical intervention (vs. no surgery)</td>
<td>57% vs. 75% (ns)</td>
<td>24% vs. 50% (p=0.21, OR:0.31)</td>
</tr>
<tr>
<td>Previous anti-TNF treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Reason discontinuation IFX1: remission vs. other</td>
<td>57% vs. 62% (ns)</td>
<td>29% vs. 29% (ns)</td>
</tr>
<tr>
<td>- Adverse events IFX1/ADA (small numbers)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>- Antibodies IFX1/ADA (small numbers)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>- Reason discontinuation ADA: primary failure vs. other</td>
<td>86% vs. 55% (p=0.20, OR:5)</td>
<td>29% vs. 32% (ns)</td>
</tr>
<tr>
<td>- Switch from ADA to IFX ≤ 1 month</td>
<td>69% vs. 50% (ns)</td>
<td>42% vs. 16% (p=0.11, OR:6.55)</td>
</tr>
<tr>
<td>- Interval without IFX ≤12 months</td>
<td>71% vs. 53% (ns)</td>
<td>36% vs. 27% (ns)</td>
</tr>
<tr>
<td>Treatment characteristics IFX2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Indication for IFX2 (luminal vs. fistulizing)</td>
<td>61% vs. 64% (ns)</td>
<td>39% vs. 18% (ns)</td>
</tr>
<tr>
<td>- Baseline CRP ≤5mg/L vs. &gt;5mg/L</td>
<td>73% vs. 59% (ns)</td>
<td>45% vs. 24% (ns)</td>
</tr>
<tr>
<td>- Induction schedule</td>
<td>56% vs. 69% (ns)</td>
<td>25% vs. 38% (ns)</td>
</tr>
<tr>
<td>- Pre-treatment corticosteroids (small numbers)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>- Concomitant immune modulators</td>
<td>65% vs. 55% (ns)</td>
<td>30% vs. 33% (ns)</td>
</tr>
<tr>
<td>- Intensified maintenance therapy at reintroduction</td>
<td>69% vs. 56% (ns)</td>
<td>38% vs. 25% (ns)</td>
</tr>
</tbody>
</table>

Table 5. Factors associated with sustained clinical benefit and clinical remission were analyzed using Fisher's exact test statistics. P values are depicted when P<0.25, ns, non-significant. OR: Odds ratio, B1, non-stricturing, non-penetrating; IFX1, 1st infliximab course; ADA, adalimumab; IFX2, infliximab retreatment.
Discussion

In the current study we evaluated the effect of IFX retreatment in CD patients who had previously been treated with IFX and ADA, consecutively. Based on this retrospective analysis, IFX retreatment appeared beneficial in the majority of CD patients for at least 18 months. Therefore, this clinical strategy may be considered as ‘rescue therapy’ before surgery or other experimental therapies are offered.

In the SWITCH trial CD patients were randomized to a switch to ADA or to continued IFX therapy. All patients were in clinical remission on IFX. Patients who switched to ADA had a less favourable outcome than those continued on IFX. Eight patients were sequentially treated with IFX-ADA and IFX in SWITCH, and this retreatment with IFX was successful in all these patients. However, IFX dose-escalation was required in 4/8 patients within one year. In this study all patients were initial responders to IFX and therefore may not be representative for daily clinical practice where patients are also switched for toxicity reasons and loss of response. We believe that our cohort represents a patient population from daily clinical practice, hence the results could offer guidance to clinicians.

In previous studies only small sub cohorts assessed the short-term clinical response of retreatment with IFX after a so called ‘drug holiday’. reported a 93% remission rate of re-treatment IFX after approximately 40 days, whereas demonstrated 48% response to IFX re-treatment. Short-term (i.e. week 14) response to reintroduction of IFX has also been studied by showing 90% clinical response. Predictors for treatment success appeared to be: reason for stopping first IFX course (remission), 0-2-6 week induction regime at restarting IFX and concomitant use with immunomodulators.

Recently reported on the short-term efficacy of IFX treatment after ADA failure in a small cohort of CD patients, but these patients were not previously exposed to IFX. Hence, the long-term clinical outcome of IFX retreatment after consecutive use of both IFX and ADA has not been reported up to now.

Our results show favourable long-term effects of IFX retreatment after previous exposure to both IFX and ADA in CD patients under certain circumstances, such as using an intensified dose as needed during the first IFX round and sometimes further dose intensification during the second round. Antibody levels to therapeutic antibody as well as serum concentrations can offer guidance to make the appropriate choices.

This cohort represents a small, but well characterized patient group with a high proportion of penetrating disease behaviour and surgical interventions prior to IFX reintroduction. The indication for IFX re-introduction was made by the treating physicians. Therefore, patients who failed the first IFX treatment course due to intolerance or adverse events, or patients in whom antibody formation was present were less likely to be prescribed the second IFX episode. Nevertheless, the cohort includes three such patients (10%).
Furthermore, not all patients were genuine ‘failures’ (i.e. loss of response or intolerance) at the time of discontinuation of the first IFX treatment. 24% of patients were in clinical remission and 10% preferred a subcutaneous route of drug administration (‘elective switch’), which might have introduced bias. Surprisingly, clinical remission rate was the same and sustained clinical benefit was comparable at 18 months follow-up between the patient subgroup in previous remission and the patients where discontinuation of first IFX treatment was otherwise specified.

None of the patient, disease or treatment related factors like re-induction, pre-treatment with corticosteroids, concomitant use of immunomodulators or intensified maintenance schedule were found to be significantly associated with sustained clinical benefit, possibly due to the limited sample size of this study. However, non-stricturing and non-penetrating disease behaviour was significantly associated with higher clinical remission rates. Furthermore, a higher likelihood of achieving clinical remission was seen in patients in whom less than one month elapsed between discontinuation of ADA and reintroduction of IFX. In patients in whom the second IFX therapy was intensified at reintroduction, higher rates of clinical remission were seen compared to patients with a stable dose, even though it was not a significant difference.

In this patient population, empiric dose escalation or shortening of treatment intervals were already done during the first IFX treatment course, and a significant proportion (45%) of patients was re-started on intensified IFX treatment. Moreover, in 38% of patients IFX dose was further escalated or treatment intervals were shortened during the second IFX course. Interestingly, 82% of these patients were able to sustain clinical benefit, whereas 45% were able to regain clinical remission. These findings are in line with previous studies that showed that dose escalation and shortening of infusion intervals are effective for regaining response in 47% to 76% of CD patients.\(^1\)\(^2\) Therapeutic drug monitoring and anti-drug antibodies were not yet routinely measured (in case of loss of response or intolerance), because the patients in our cohort received their first IFX treatment in the ‘early anti-TNF era’. However, evidence suggests that IFX antibody levels decline to undetectable levels within one year after cessation of IFX therapy.\(^3\)

Whereas in Europe only two anti-TNF agents are available for the treatment of CD, for rheumatological indications several monoclonal antibodies have been approved. In rheumatoid arthritis it has been shown that introducing a second anti-TNF antibody can maintain response or restore initial response in patients with a loss of response to the first anti-TNF agent.\(^4\)\(^3\) However switching to a drug with a different mode of action (rituximab) appeared to be even more effective than the second anti-TNF therapy in patients with rheumatoid arthritis.\(^4\)\(^4\) Switching to a second or even a third anti-TNF agent had a satisfactory response in approximately 4 out of 5 spondyloarthropathy patients.\(^4\)\(^5\) At least one
third of ankylosing spondylitis patients show a favourable clinical response after switching to a second anti-TNF inhibitor and more than half of the patients continued on the second therapy for more than 2 years.48

In conclusion, this retrospective cohort study shows that IFX reintroduction has long-term beneficial effects in the majority of CD patients with a history of previous consecutive IFX and ADA treatment. Therefore, repeated IFX treatment is to be considered a valuable strategy in this group of highly refractory CD patients.
REFERENCES


