Low Discontinuation Rate of Infliximab Treatment in Steroid-Dependent/Refractory Crohn's Disease Patients

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Keywords

Crohn's disease · Fecal calprotectin · Infliximab · Relapse · Remission

Abstract

Background: Many patients with moderate to severe Crohn's disease (CD) are treated with infliximab (IFX). As most of these patients experience a long-lasting therapy, the outcome and withdrawal of IFX treatment are important clinical questions. **Methods:** In this retrospective study, we analyzed the treatment outcome in moderate to severe CD patients with a steroid-dependent/refractory disease course started on IFX. Withdrawal of IFX was evaluated in patients with deep remission defined as clinical (Harvey-Bradshaw Index ≤ 4), biochemical (fecal calprotectin [FC] ≤ 150 $\mu\text{g/g}$ stool) over a period of 2 years, and endoscopic and histological remission before discontinuation of IFX. **Results:** After induction with IFX, clinical remission was observed in 45/109 patients (41.3%) and clinical response in 61/109 patients (56.0%). Only 8/109 patients (7.3%) achieved deep remission and therefore could be discontinued from IFX therapy. In 4 of these patients (50%), relapse was observed after discontinuation of IFX treatment. FC decreased in these 8 patients in deep remission from 652 ± 168 $\mu\text{g/g}$ stool (mean $\pm$ SE) at baseline to 24.9 ± 8.1 $\mu\text{g/g}$ stool at 14 weeks. When com-

pared to patients in deep remission, FC had decreased significantly less at 14 weeks in patients in clinical remission after induction with IFX ($n = 31$; 154 ± 55 $\mu\text{g/g}$ stool; $p = 0.01$), in patients with clinical response after induction achieving clinical remission during the maintenance phase ($n = 11$; 352 ± 67 $\mu\text{g/g}$ stool; $p = 0.004$), or in patients with chronic active disease course on maintenance therapy ($n = 50$; 645 ± 93 $\mu\text{g/g}$ stool; $p < 0.001$). **Conclusion:** A low discontinuation rate was observed for steroid-dependent/refractory moderate to severe CD patients with IFX treatment. As FC showed a more or less pronounced decrease depending on the response to the IFX treatment, monitoring of FC may become a noninvasive tool for tailoring biological therapy in CD patients.

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Introduction

Crohn's disease (CD) is a chronic inflammatory condition of the gut characterized by periods of remission and episodes of relapse. Clinical relapses in inflammatory bowel disease (IBD), especially in CD, are difficult to predict. The tumor necrosis factor- α (TNF α) antagonist in-

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fliximab (IFX) is currently a main cornerstone in the treatment to induce and maintain remission in patients with moderate to severe CD. However, despite clinically defined successful treatment, endoscopically and histologically detectable inflammation may occur.

The lack of clear recommendations for the discontinuation of TNF α -blocking therapy may lead to long-term maintenance treatment, raising questions about safety and economic issues. As IFX is an expensive treatment with potential side effects, the outcome of stopping IFX is an important question.

In clinical practice, the decision whether to continue or discontinue treatment in patients in deep remission is still very much based on assessment of the patient's individual risks and benefits. Existing guidelines have concluded that because of limited evidence, no recommendations can be made on when and in whom to discontinue TNF α -blocking therapy after having obtained clinical remission [1]. Currently, withdrawal of biological therapy is suggested in CD patients who have both complete mucosal healing and no biological evidence of inflammation [2, 3]. However, several studies have shown that a substantial number of patients with IBD in stable remission relapsed within 2 years after stopping TNF α -blocking therapy. Notably, these studies found risk factors such as short duration of remission, previous surgical operations, high inflammation markers, and endoscopically active disease as of prognostic importance in predicting a higher risk of relapse [4–6].

Fecal calprotectin (FC), a by now commonly used biomarker of intestinal inflammation, is secreted into the intestinal lumen during cell activation and death from activated leukocytes, mainly neutrophils, and can be detected in stool [7, 8]. Several studies have shown that measurement of FC may indicate clinical relapse in asymptomatic patients with IBD, especially in ulcerative colitis and colonic CD [9, 10]. Importantly, FC correlates not only with clinical disease activity, but also with endoscopic and histological inflammation in IBD patients [11–13]. FC seems to be more sensitive than the Crohn's Disease Activity Index (CDAI) or C-reactive protein to detect endoscopic inflammation [13, 14] and therefore is a reliable surrogate marker of mucosal healing in patients with CD [15, 16].

Recent data showed that a normal FC concentration after induction with TNF α -blocking therapy predicts sustained clinical remission in the majority of IBD patients on maintenance therapy for active luminal disease [17]. These data suggest an important role of FC in monitoring IBD patients during immunosuppressive therapy, but

also during remission. The aim of this study was to evaluate long-term IFX treatment outcome and IFX withdrawal in steroid-dependent/refractory moderate to severe CD patients with deep remission.

Subjects and Methods

Study Population

In this retrospective single-center cohort study, all CD patients who received induction of IFX therapy at the Department of Gastroenterology and Hepatology of the University Hospital Basel from January 2008 to October 2015 for a steroid-dependent, steroid-refractory, or complicated disease course were analyzed. Steroid dependency and refractoriness were defined as symptom recurrence due to decrease in steroid dosage below the Cushing threshold of 7.5 mg prednisone/day or symptom persistence despite systemic steroid therapy above this threshold. Complicated disease course was defined as the occurrence of stenosis/strictures, fistulae, abscesses, extraintestinal manifestations (EIMs), or the necessity for surgery. Seven patients were excluded from the study because they received a top-down therapy scheme. In patients who were lost to follow-up due to referral to other hospitals or for other reasons, the date of last contact with the University Hospital Basel was considered as the end of the follow-up period. All patients are enrolled in the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), a national prospective clinical cohort started in 2006 that was approved by the local ethics committee (EKBB 193/06).

Data Collection

All medical charts were retrospectively reviewed. Patient characteristics, disease characteristics, and laboratory parameters (e.g., FC) were assessed in every patient at the time of IFX initiation, every 2–6 months during the treatment period, and after IFX discontinuation in patients with deep remission. The Harvey-Bradshaw Index (HBI) was assessed by the physician in charge. Induction treatment (IFX 5 mg/kg) was defined as three infusions within a period of 6 weeks. Maintenance therapy was defined as a permanent scheduled therapy scheme. In general, maintenance therapy was started with a schedule of IFX 5 mg/kg every 8 weeks. In a substantial number of patients, an intensification of therapy was necessary to achieve or maintain remission. Therapy intensification was defined as adaption of IFX application interval and/or dosage and was adjusted individually for each patient by the physician in charge.

Endpoints and Assessments

The primary endpoint of the study was assessment of the percentage of moderate to severe CD patients achieving deep remission under IFX treatment and of the success of discontinuation of IFX. In order to be discontinued from IFX therapy, patients had to be in deep remission, defined as clinical and biochemical remission during an observation period of ≥ 2 years and endoscopic and histological remission before discontinuation of IFX [3]. Endoscopic and histological remission was defined as complete mucosal healing. Clinical remission was defined as a CDAI score ≤ 150 points or a HBI score ≤ 4 points. Biochemical remission in our evaluation was defined as FC ≤ 150 $\mu\text{g/g}$ stool [18, 19]. FC was measured by Rothen Medical Laboratories AG, Basel, Switzerland using the Bühlmann

fCAL™ ELISA (Bühlmann Laboratories AG, Schönenbuch, Switzerland). Clinical response was defined as a reduction in the CDAI score ≥ 70 points or in the HBI score ≥ 3 points.

Furthermore, relapse after discontinuation and change of treatment was assessed. Change of treatment was defined as replacement of TNF α inhibitor or switch to a different biological due to primary nonresponse after induction, loss of response, antidrug antibodies, or adverse events.

The success of retreatment with IFX or adalimumab was evaluated in patients who relapsed after discontinuation of IFX treatment.

Statistical Analysis

The results were given as percentages, as median and range in case of non-normally distributed data, or as mean $\pm$ SE for normally distributed data. A Kaplan-Meier survival analysis was performed to determine the time to relapse in deep remission patients discontinued from IFX treatment. For analysis of FC values, the following study groups were compared to the deep remission group during the time course of 96 weeks: (1) clinical remission after induction with IFX, (2) clinical response after induction achieving clinical remission during the maintenance phase, and (3) chronic active disease course under maintenance therapy. Because of the distinct baseline FC values present in the four study groups, relative FC values were calculated. In order to compare the study groups with the deep remission group at the three given time points, a linear mixed-effects model with log-transformed FC values was performed. The resulting estimates were ratios (the reference being deep remission) with the corresponding 95% confidence intervals and *p* values. A *p* value < 0.05 was considered significant. All analyses were performed with the statistical program R version 3.1.2.

Results

Patient Characteristics

From 116 patients treated for CD between 2008 and 2015 at the University Hospital Basel receiving IFX induction therapy with at least three infusions, 109 patients were included in this study. The baseline characteristics and prior medications of the 109 patients are shown in Table 1. The median age at start of IFX therapy was 36 (range 15–77) years, with a median disease duration of 5 (range 0.1–38) years.

IFX Induction Therapy

In Figure 1, a treatment tree for CD patients with a steroid-refractory or steroid-dependent disease course started on IFX is illustrated. The first division in the treatment tree shows that 45/109 patients (41.3%) achieved clinical remission and 61/109 patients (56.0%) achieved clinical response after induction treatment with IFX. Due to primary nonresponse to IFX after induction, a direct change of treatment was necessary in 3/109 patients (2.7%).

Table 1. Baseline characteristics of Crohn's disease patients with IFX induction therapy

Sex (male/female)	53/56
Montreal classification	
Age (A1/A2/A3)	13/74/22
Location (L1/L2/L3/L4)	24/30/53/17
Behavior (B1/B2/B3/+p)	46/31/34/31
Extraintestinal manifestations	
Yes/no	43/66
Arthralgia	35
Cutaneous	8
Uveitis/conjunctivitis/episcleritis	5
Age at start of IFX	36 (15–77)
Disease duration (years) at start of IFX	5 (0.1–38)
C-reactive protein (mg/L) at start of IFX	7.2 (0.3–196.2)
FC (μ g/g stool) at start of IFX	600 (10–1,500)
Albumin (mg/L) at start of IFX	35 (17–44)
CDAI score at start of IFX	212.5 (40–653)
Harvey-Bradshaw Index at start of IFX	8 (0–18)
Past medications before IFX	
Cortisone	109 (100%)
Azathioprine	76 (69.7%)
6-Mercaptopurine	7 (6.4%)
5-Aminosalicylates	33 (30.3%)
Methotrexate	9 (8.3%)
Adalimumab	11 (10.1%)
Antibiotics	22 (20.2%)

Values are presented as *n*, *n* (%), or median (range). CDAI, Crohn's Disease Activity Index; FC, fecal calprotectin; IFX, infliximab.

Patients in Clinical Remission after Induction Therapy with IFX

Of the 45 patients in clinical remission after induction therapy with IFX, 31 remained on maintenance IFX therapy, receiving IFX injections every 8 weeks with potential adaption of application interval and dosage. Adjustment of IFX application was carried out in case of inflammatory activity between drug administration intervals with FC values > 150 μ g/g stool without overt clinical symptoms. In 5 of these 31 patients (16.1%), a change to a different TNF α inhibitor was needed, and another 5 (16.1%) needed a therapy intensification. Six out of 45 patients (13.3%) initially in remission after IFX induction were lost to follow-up. Deep remission was achieved in 8 patients and IFX was discontinued in these cases.

Patients with Clinical Response after Induction with IFX

In 11/61 patients (18%) clinical remission was achieved during maintenance treatment. In 4 of these 11 patients

Fig. 1. Treatment decision tree for Crohn's disease patients ($n = 109$) with clinical remission or clinical response after IFX induction therapy. ADA, adalimumab; FU, follow-up; IFX, infliximab; TNF α , tumor necrosis factor- α .

this was achieved with an unchanged therapy regimen and in 7 with an intensified IFX treatment. However, none of these patients fulfilled the cessation criteria of clinical and biochemical remission during an observation period of ≥ 2 years, and therefore all remained on continuous IFX maintenance therapy.

In 50/61 patients (82.0%), after induction and during maintenance IFX therapy only a clinical response could be achieved. These patients remained in a chronic active state, and therapy intensification was necessary in 35 patients, with dosage increase in 2/50 patients (4%), interval shortening in 20/50 patients (40%), and both options in 13/50 patients (26%). Despite clinical and immediate biochemical response after IFX application, these patients did not achieve biochemical remission. A switch to an alternative TNF α inhibitor was performed in 15/50 patients (30%).

Discontinuation of IFX Therapy

In total, 8/109 patients (7.3%) initially started on IFX treatment achieved deep remission and could be discontinued from IFX therapy. Importantly, no patient with EIMs achieved deep remission and could be withdrawn from IFX treatment. The course of therapy of these 8 patients after IFX discontinuation is depicted in Figure 2. The FC values and HBI scores of the 8 patients with deep remission during IFX treatment and after discontinuation of treatment are shown in Figure 3a and b. Arrows indicate the time points of discontinuation for patients with relapse ($n = 4$), which occurred at a median of 11 (range 3–17) months after cessation of IFX therapy. Of those, the first patient was discontinued 25 months after IFX had been started and experienced a relapse 16 months after the last infusion; the second patient interrupted IFX after 32 months and relapsed 6 months after the last IFX infusion; the third stopped IFX after 36 months and relapsed 3 months after discontinuation.

Fig. 2. Treatment decision tree for Crohn's disease patients discontinued from IFX therapy during the course of maintenance treatment. ADA, adalimumab; IFX, infliximab.

The fourth patient experienced relapse 17 months after IFX discontinuation. Time to relapse is shown in a Kaplan-Meier curve (Fig. 3c). In 2/4 patients an FC increase prior to clinical symptoms indicated relapse, whereas in the other 2 patients FC measurement was carried out as relapse had already become obvious by clinical symptoms.

The other 4 patients remained in remission after cessation of IFX with a median remission duration of 23.5 (range 16–70) months. Their FC levels fluctuated between 20 and 120 $\mu\text{g/g}$ stool after IFX cessation without clinically overt symptoms. These patients were considered in remission without any medical treatment at the end of the observation period.

Restart of IFX Therapy

Patients with a relapse after discontinuation of IFX therapy achieved clinical remission after reinduction with anti-TNF α treatment. In 3 patients remission was achieved after reinduction with IFX and in 1 patient after a switch to adalimumab (Fig. 2). No serious adverse events or infusion reactions were reported in the retreated patients during the follow-up.

FC Monitoring during IFX Therapy

We analyzed FC behavior before, within, and after 96 weeks of IFX therapy (Fig. 4). FC measurement showed that in the deep remission group, FC decreased after induction therapy from 652 ± 168 $\mu\text{g/g}$ stool (mean $\pm$ SE)

at baseline to 24.9 ± 8.1 $\mu\text{g/g}$ stool at 14 weeks and remained low during the following maintenance treatment with IFX. During the disease course, patients in the group classified as clinical remission after induction with IFX ($n = 31$) demonstrated FC values similar to those of patients who did not achieve remission initially after induction therapy ($n = 11$). In the remission group after induction with IFX ($n = 31$), FC was 667 ± 155 $\mu\text{g/g}$ stool (mean $\pm$ SE) at baseline, 154 ± 55 $\mu\text{g/g}$ stool at 14 weeks, and 167 ± 83 $\mu\text{g/g}$ stool at 96 weeks. Patients in remission with clinical response after IFX induction ($n = 11$) showed an FC of $1,015 \pm 267$ $\mu\text{g/g}$ stool (mean $\pm$ SE) at baseline, which decreased to 352 ± 67 $\mu\text{g/g}$ stool at 14 weeks and to 85 ± 14 $\mu\text{g/g}$ stool at 96 weeks. Patients with chronic active disease course during maintenance treatment ($n = 50$) showed an initial FC of $1,067 \pm 86$ $\mu\text{g/g}$ stool (mean $\pm$ SE) at baseline, which significantly dropped to 645 ± 93 $\mu\text{g/g}$ stool at 14 weeks, but persisted throughout the observation period at higher values of 606 ± 104 $\mu\text{g/g}$ stool at 48 weeks and of 800 ± 98 $\mu\text{g/g}$ stool at 96 weeks.

When compared to patients in deep remission at 14 weeks, FC decreased significantly less in patients in clinical remission after induction with IFX, in patients achieving clinical remission on maintenance therapy with clinical response after induction, and in patients with chronic active disease course on maintenance therapy (Fig. 4; online supplementary Table 1, see www.karger.com/doi/10.1159/000486676).

Fig. 3. **a, b** FC values (µg/g stool) (**a**) and HBI scores (**b**) of patients discontinued from IFX during the course of maintenance treatment. Open symbols show patients with continuous remission after stopping IFX, full symbols patients with relapse. Arrows indicate the time points of discontinuation for patients with relapse. **c** Kaplan-Meier analysis showing time to relapse for patients in deep remission ($n = 8$) after withdrawal of IFX. FC, fecal calprotectin; HBI, Harvey-Bradshaw Index; IFX, infliximab.

Fig. 4. Comparison of FC values (µg/g stool) in Crohn's disease patients during the disease course. Patients with deep remission are compared to patients with remission on maintenance therapy and chronic active disease course at baseline, 14 weeks, 48 weeks, and 96 weeks of treatment. FC values are shown as mean $\pm$ SE. For statistical analysis relative FC values were calculated, and for comparison of the study groups versus patients in deep remission (discontinued from IFX) a linear mixed-effects model with log-transformed FC values was used. BL, baseline; FC, fecal calprotectin; IFX, infliximab.

Switch from IFX to Another TNF α Antagonist

In 23 subjects a switch from IFX to another TNF α antagonist was performed. Withdrawal of IFX in 11 patients was necessary due to therapy failure, development of antibodies to IFX in 4 patients, or side effects (cutaneous reactions, dyspnea, and headache) of IFX in 8 patients.

Discussion

To date, there are no established guidelines on whether and when IFX can be interrupted safely in IBD patients with long-standing remission [1, 3, 20, 21].

Relapse after discontinuation of anti-TNF α treatment has been shown for 44% of CD patients and for 38% of ulcerative colitis patients, largely depending on the presence or absence of mucosal healing [22]. Although retreatment with IFX due to relapse is effective and well tolerated, a relevant nonresponse rate of 19% in CD and 46% in ulcerative colitis was reported [23].

Our data demonstrate similar findings with comparable remission rates for CD patients treated with IFX [24]. However, only a minority of CD patients with deep remission in our center, who were started on IFX therapy due to steroid-dependent, steroid-refractory, or complicated disease course, could be successfully discontinued from TNF α inhibitor treatment. Survival analysis revealed that 6/8 (75%) of our patients remained in clinical remission 12 months after cessation, which corresponds to recently published results [6, 25, 26]. Similarly and also in accordance to published data, discontinued patients with relapse showed a good response to either IFX reinduction or to adalimumab treatment [19, 27].

There is a current belief that the risk of disease relapse after cessation of anti-TNF α therapy may be minimized using predictors that identify patients with a relevant risk of relapse. Recently, it was demonstrated that undetectable anti-TNF α drug levels in patients with long-term remission predict successful drug withdrawal, as clinical remission was no longer dependent on the anti-TNF α agent [28]. However, this information is not available for our patients, as IFX drug monitoring was not yet performed when the first patients were included in this analysis and currently in our center IFX drug levels and anti-IFX antibodies are only assessed in patients not responding to treatment.

FC may be another potential candidate, since FC concentration in stool seems to be a reliable parameter of mucosal inflammatory activity in IBD and also appeared to be a good marker for predicting clinical relapse [29–33]. A recent study reported a 4-fold increase in CD with an FC level >200 $\mu\text{g/g}$ stool [34]. Moreover, the cutoff value for FC of >150 $\mu\text{g/g}$ stool has been shown to be a strong predictive marker of relapse in CD [29]. In addition, normal FC concentration after induction therapy with TNF α -blocking therapy predicts sustained clinical remission in the majority of IBD patients on maintenance therapy for active luminal disease [17]. Other authors report that an FC level <150 $\mu\text{g/g}$ stool could be indicative for deep remission [13, 18, 19]. Interestingly, this is confirmed in our cohort, as only patients who achieved an FC value ≤ 150 $\mu\text{g/g}$ stool after IFX induction therapy later qualified for discontinuation from TNF α treatment. Therefore, FC measurement during the disease course has a potential predictive value for withdrawal of IFX in CD patients with deep remission and for reinduction of anti-TNF α therapy after biochemical relapse.

Another important question for discussion will be when during the disease course mucosal healing as a mea-

sure of sustained clinical remission – defined as absence of symptoms and no corticosteroids for >6 months – should be evaluated [35]. Previous studies have suggested that the absence of mucosal healing at the time of discontinuation of biological therapy predicted a relapse [36]. However, it was recently demonstrated that mucosal healing does not predict “sustained” clinical remission if the biologicals are stopped after 1 year of treatment [23]. In our cohort, patients were evaluated for mucosal healing using colonoscopy before discontinuation if clinical and biochemical assessment indicated sustained clinical remission.

As in over 90% of our study population IFX could not be interrupted, we support the hypothesis of a continuous anti-TNF α therapy in steroid-dependent/refractory CD patients. In agreement with our results, Bortlik et al. [19] recently showed that even deep remission at the time of anti-TNF withdrawal does not prevent relapse in CD patients. The authors’ findings emphasize that there might be factors other than endoscopy and clinical remission that could reflect disease activity. One of these clinical factors might be reflected by EIMs as these patients tend to have a more severe disease course and as none of the patients with EIMs could be discontinued from IFX in our cohort.

This study has several limitations. First, the low primary nonresponse rate after induction treatment may be reflected by the retrospective nature of the analysis. Some patients in the clinical response group with borderline clinical response at week 14 may have received more infusions and therefore not classified as primary nonresponders after the induction phase. Second, the small number of patients who finally achieved deep remission may be explained with long disease duration (median of 5 years) before initiation of IFX therapy, but also with a very strict selection of patients with steroid-dependent/refractory disease course in this analysis. In addition, another 42/109 patients (38.5%) were considered to be in clinical remission, but based on nonpersistent clinical (HBI score ≤ 4 points) and biochemical (FC ≤ 150 $\mu\text{g/g}$ stool) remission during ≥ 2 years of observation, these patients were not offered discontinuation from the drug. As they were not evaluated endoscopically, it cannot be excluded that discontinuation could have been attempted in some of them. Thus, our data may vary from those of other centers depending on the selection of patients started on IFX and stage and severity of the disease. Finally, we did not apply a top-down strategy.

In conclusion, due to the chronic nature of this disease, CD subjects should be well informed about the potential

long-standing therapy before beginning treatment with a TNF α inhibitor. Although cessation of a biological therapy is a very important issue for patients with CD, our data demonstrate only a minimal discontinuation rate for patients with moderate to severe disease course. Moreover, a relapse rate of 50% in patients with deep remission discontinued from anti-TNF α therapy emphasizes the chronic character of CD and the prevalent belief of anti-TNF α treatment as a long-standing therapy. Biochemical relapse prior to clinical relapse and the correlation with mucosal healing indicate that FC, together with the consideration of the patient's general condition and clinical activity, may become a noninvasive tool for monitoring the inflammatory course of CD and a helpful decision tool for tailoring biological therapy in CD.

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Statement of Ethics

All patients are enrolled in the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), a national prospective clinical cohort started in 2006 that was approved by the local ethics committee (EKBB 193/06).

Disclosure Statement

All authors declare that they have no financial or nonfinancial competing interests in or benefits from this project. This study did not receive any funding.

Author Contributions

T. Kaymak, F. Moriconi, and P. Hruz gathered the data. T. Kaymak and P. Hruz analyzed and interpreted the data. The manuscript was drafted by T. Kaymak, F. Moriconi, and P. Hruz and reviewed for content by J.H. Niess and C. Beglinger. All authors read and approved the final manuscript.

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