Long-term outcome after infliximab for refractory ulcerative colitis

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Abstract

Background and aims: Infliximab (IFX) has been shown efficacious for moderate-to-severe ulcerative colitis (UC), but data on long-term efficacy are lacking. We investigated long-term outcome including colectomy rates in outpatients treated with IFX for refractory UC in a single referral centre, and evaluated if predictors could be identified.

Methods: The first 121 outpatients (median age 38.0 years) with refractory UC treated with IFX were included. The primary outcome was colectomy-free survival. Secondary measures were sustained clinical response and serious adverse events.

Results: From the 81 patients (67%) with an initial clinical response to IFX, 68% had a sustained clinical response. No independent predictors of sustained clinical response could be identified. Over a median (IQR) follow-up period of 33.0 (17.0–49.8) months, 21 patients (17%) came to colectomy. Independent predictors of colectomy were absence of short-term clinical response [Hazard ratio 10.8 (95% CI 3.5–32.8), p<0.001], a baseline CRP level ≥5 mg/L [Hazard ratio 14.5 (95% CI 2.0–108.6), p=0.006] and previous IV treatment with corticosteroids and/or cyclosporine [Hazard ratio 2.4 (95% CI 1.1–5.9), p=0.033]. Six patients developed a serious infection, three a malignancy, two a post-operative complication and one patient died (suicide).

Keywords: Inflammatory bowel disease; Ulcerative colitis; Infliximab; Anti-TNF; Outcome; Colectomy; Predictor

Abbreviations: ACT, active ulcerative colitis trial; CI, confidence interval; IFX, infliximab; IQR, interquartile range; IV, intravenous; MDR1, multidrug resistance gene 1; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; UC, ulcerative colitis.

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1. Introduction

Ulcerative colitis (UC) is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon, rectal bleeding, diarrhoea and abdominal pain. The majority of patients with UC can be treated successfully with 5-aminosalicylates, corticosteroids and/or immunomodulators. Recently, the randomized double-blind multi-centre placebo-controlled ACT1 and ACT2 trials clearly showed a significant benefit of infliximab (IFX) in patients with moderate-to-severe active UC. At weeks 8, 30 and 54, patients receiving IFX had significant higher clinical response and remission rates, achieved mucosal healing more frequently and were more often able to stop corticosteroids. Long-term outcome data, including data on colectomy rates, are lacking.

We previously reported the short-term outcome of IFX in patients with refractory UC from our centre. The aim of this study was to describe long-term clinical outcome in a consecutive cohort of 121 outpatients who received IFX for refractory UC in a single referral centre, and to investigate if predictors of sustained clinical response and colectomy could be identified.

2. Methods

2.1. Patient population

All patients with refractory UC who received a first infusion with IFX before November 2006 were included in this study, allowing a follow-up of at least 6 months. Nine patients with acute severe IV steroid-refractory colitis were excluded, since analysis of this small subgroup was considered not meaningful. Eligible patients did not respond to corticosteroids alone, immunomodulators alone, or a combination of both, were intolerant to any of these drugs or were unable to taper corticosteroids. We identified 121 patients (42% female), with a median (interquartile range, IQR) age at first IFX of 38.0 (27.4–52.0) years. Patients’ characteristics are listed in Table 1.

Thirty patients received their first IFX infusion as part of ACT1. The remaining patients received IFX in a compassionate use program, including 12 patients randomized to placebo during ACT1.

Based on a previously reported association with need for colectomy, we assessed presence of polymorphisms in the multidrug resistance gene 1 (MDR1) by PCR-RFLP. All individuals gave informed consent and this study was approved by the local ethics committee of the Catholic University of Leuven.

2.2. Definitions

Extent of disease was categorized using the Montreal classification. Severity of disease prior to IFX was determined according to the Mayo endoscopic subscore in 102 patients. Patients were considered active smokers, if they had been actively smoking more than seven cigarettes a week, for at least 6 months.

Short-term response to IFX was assessed after 4 weeks in patients who received a single infusion, and after 10 weeks in patients who received an induction scheme with IFX at weeks 0, 2 and 6. Short-term clinical response was defined as

Conclusions: With a median follow-up of 33.0 months after start of IFX, 17% of patients with refractory UC needed colectomy, while sustained clinical response was present in 68% of initial responders.

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Long-term outcome after IFX for refractory UC

complete if there was absence of diarrhoea and blood, and partial if there was marked clinical improvement but still persistent rectal blood loss. To assess short-term mucosal healing, endoscopy was performed in 70 patients both prior to and 4 or 10 weeks after first IFX infusion. Mucosal healing was defined as a Mayo endoscopic subscore of 0 or 1, and was only assessed in patients with a Mayo endoscopic subscore of at least 2 at inclusion. Short-term CRP drop was analyzed in patients with elevated CRP at baseline if a second CRP level was available 4–10 weeks after first IFX infusion. A significant short-term CRP drop was defined as a decrease of more than 50% or a normalization (<5 mg/L).

Sustained clinical response was defined as persistent clinical improvement during follow-up without need for new courses of corticosteroids or any other systemic drug (cyclosporine, azathioprine, methotrexate, investigational drugs), and was only assessed in patients who achieved an initial clinical response. Colectomy-free survival was defined as absence of colectomy, regardless of clinical findings and need for other medical interventions.

Serious adverse events were defined as any event that resulted in hospitalization or prolonging of hospitalization, was life threatening or leaded to significant disability. Serious infections were defined like-wise. Acute infusion reactions were defined as any adverse experience that occurred during or within 1 h after IFX infusion, and serum-sickness-like reaction was defined as occurrence of myalgia, arthralgia, fever and/or rash between 1 and 14 days after IFX infusion. Short-term post-operative complications included anastomotic leaks, pelvic abscesses and wound infections which occurred within the first 30 days after surgery.

2.3. Administration of infliximab

At start, patients received either a single dose of 5 or 10 mg IFX per kg bodyweight, or an induction scheme with IFX at weeks 0, 2 and 6. The majority of patients showing clinical response (75%), received maintenance therapy thereafter with IFX therapy every 8 weeks. The remaining patients received episodic therapy. The decision for induction and/or maintenance therapy was based on study guidelines (for patients included in ACT1) or disease activity and availability of the drug (for other patients).

2.4. Statistics

All statistical analyses were performed using the SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.1 statistical software packages (SAS Institute Inc., Cary, NC, USA). Colectomy-free survival and sustained clinical response were estimated by Kaplan–Meier analyses. We used both Breslow and LogRank tests to compare hazard rates in populations defined by one variate at the time. Since length of follow-up varied significantly between patients, the most appropriate test to look for predictors is the Breslow test, also known as Gehan Wilcoxon test, where time points are weighted by number of cases at risk at each time point. However, we also included the most commonly used LogRank test, were all time points are weighted equally. This test has optimal power to detect alternatives where hazard rates in populations are proportional to each other. A Cox proportional hazards survival regression including all variables with Breslow


p<0.100, was performed to identify independent predictors. We checked departures from the proportional hazards model by introducing time-dependent explanatory variables, using log(t) multipliers and adjustments by the average of the logs (0.5). There was no indication that the proportionality of hazard assumption was violated. The smallest p-value obtained for each variable separately was 0.106.

To analyze the effect of IFX in typical daily clinical practice, we also analyzed the data in a subgroup of 91 outpatients with refractory UC who received their first IFX infusion outside ACT1.

3. Results

During a median (IQR) follow-up of 33.0 (17.0–49.8) months, a total of 1086 infusions of IFX were administrated, with a median (range) of 5 (1–41) infusions per patient. As shown in Table 1, 39 patients received an induction scheme with IFX at weeks 0, 2 and 6. At start 43% of patients were taking corticosteroids.

3.1. Short-term clinical and endoscopic response

Overall, 63% of 121 UC patients treated with IFX showed short-term clinical response. In more detail, 41% patients had complete, 22% had partial and 37% lacked short-term clinical response. Analysis of the subgroup of 91 UC patients who received IFX for refractory colitis outside ACT1 yielded similar results (40% complete and 22% partial short-term clinical response).

Short-term mucosal healing was only assessed in 70 patients (58%). Overall, 53% achieved short-term mucosal healing. In the subgroup, 43% of 40 patients achieved short-term mucosal healing.

From the 45 patients with absence of short-term clinical response in the overall cohort, one patient who received the induction scheme achieved clinical response after a fourth infusion and four patients who did not receive the induction scheme achieved clinical response after a second infusion. In total, 81 patients (67%) achieved clinical response to IFX at a certain time.

3.2. Infliximab regimen

From the 81 patients achieving clinical response, five stopped IFX since it had been introduced as bridging therapy for immunosuppressive agents which were introduced simultaneously with IFX. Two patients stopped IFX because of important infusions reaction during both the second and third administration despite appropriate prophylaxis. One patient achieved complete clinical response after a single infusion and was not treated with anti-TNF thereafter. From the remaining 73 patients, 75% received maintenance therapy with IFX every 8 weeks (Table 1). In 12 of them the dose had to be increased. In 17 patients under maintenance therapy the interval of IFX administration had to be shortened to every seven (n=2), six (n=10), five (n=1) or four weeks (n=4).

3.3. Sustained clinical response

From the 81 patients achieving clinical response, 68% had a sustained clinical response during a median (IQR) follow-up of 33.4 (17.0–51.1) months (Fig. 1A). In univariate analysis, predictors for sustained clinical response were a significant
short-term CRP drop (Breslow \( p = 0.034 \), LogRank \( p = 0.043 \)) and extensive colitis at baseline (Breslow \( p = 0.075 \), LogRank \( p = 0.044 \)). Patients with concomitant use of immunosuppressive agents had a trend towards a better sustained clinical response (Breslow \( p = 0.066 \), LogRank \( p = 0.061 \)). In Cox proportional hazards survival regression, however, these variables did not reach statistical significance.

From the 51 patients who were on steroids at moment of first IFX, 27 (53%) were able to stop corticosteroids during treatment with IFX.

In the subgroup of patients receiving IFX for refractory colitis outside ACT1, 67% had a sustained clinical response during a median (IQR) follow-up of 23.3 (13.3–46.6) months (Fig. 1B).

### 3.4. Colectomy-free survival

During a median (IQR) follow-up of 33.0 (17.0–49.8) months, 21 patients (17%) came to colectomy (Fig. 2A). The median (IQR) time to colectomy was 7.6 (2.4–20.7) months. Fifteen of these patients received IFX for refractory colitis outside ACT1 (Fig. 2B).

Kaplan–Meier analysis revealed absence of short-term clinical response, absence of short-term mucosal healing, a baseline CRP level \( \geq 5 \text{mg/L} \), absence of significant short-term CRP drop, previous IV treatment with corticosteroids and/or cyclosporine, and a TT genotype at MDR1 C3435T as predictors of need for colectomy (Fig. 3A–F). We analyzed previous use of IV treatment with corticosteroids and cyclosporine together, since separately both showed a trend towards a predictive role (data not shown). Interestingly, none of the nine patients who were active smokers during IFX therapy needed colectomy (Breslow \( p = 0.177 \); LogRank \( p = 0.160 \)).

Neither IFX regimen nor use of concomitant therapy was significantly associated with need for colectomy. Patients under treatment with corticosteroids at baseline showed a slight trend for higher colectomy need (Breslow \( p = 0.219 \); LogRank \( p = 0.134 \)). Regarding the association with MDR1
Figure 3  Colectomy-free survival after first IFX infusion stratified by short-term clinical response (A), short-term mucosal healing (B), baseline C-reactive protein level (C), short-term CRP drop (D), previous treatment with IV corticosteroids and/or cyclosporine (E), and MDR1 C3435T genotype (F).
C3435T, we found a significantly higher median (IQR) dose of steroids at baseline in patients with the TT genotype compared to patients with the CC or CT genotype [8 (0–16) vs. 0 (0–4) mg, Mann–Whitney p = 0.001]. The median (IQR) baseline CRP level was significantly higher in patients who underwent surgery compared to the others [17.8 (9.0–44.0) vs. 4.1 (1.5–20.5) mg/L, Mann–Whitney p = 0.001].

For the Cox proportional hazard survival regression we included all variables which showed a trend (Breslow p < 0.100) for a predictive value in univariate analysis, i.e. absence of short-term clinical response, a baseline CRP level ≥5 mg/L, previous IV treatment with corticosteroids and/or cyclosporine, a TT genotype at MDR1 C3435T and a TT genotype at MDR1 G2677T/A. Since we only had data on short-term mucosal healing and CRP drop available in, respectively, 58% and 50% of patients, we did not include these variables. By doing this, we avoided results which would not be representative for the whole cohort. Furthermore, we found a close relation between short-term mucosal healing, short-term CRP drop and short-term clinical response (all p < 0.020), and the latter variable was included in the Cox proportional hazard survival regression.

The Cox proportional hazard survival regression, identified absence of short-term clinical response [Hazard ratio 10.8 (95% confidence interval, 95% CI 3.5–32.8), p < 0.001], a baseline CRP level ≥5 mg/L [Hazard ratio 14.5 (95% CI 2.0–108.6), p = 0.006] and previous IV treatment with corticosteroids and/or cyclosporine [Hazard ratio 2.4 (95% CI 1.1–5.9), p = 0.033] as independent predictors of need for colectomy.

The same factors were identified as independent predictors of colectomy in the subgroup of 91 patients who received IFX for refractory UC outside ACT1: absence of short-term clinical response [Hazard ratio 29.9 (95% CI 3.8–233.3), p = 0.001], a baseline CRP level ≥5 mg/L [Hazard ratio 10.5 (95% CI 1.4–81.0), p = 0.024] and previous IV treatment with corticosteroids and/or cyclosporine [Hazard ratio 4.6 (95% CI 1.6–13.4), p = 0.006].

3.5. Adverse events

Thirteen patients developed an acute infusion reaction after a median (range) of 2 (1–7) infusions. Delayed hypersensitivity reactions were diagnosed in eight patients after a median (range) of 3 (2–11) infusions, and lead to discontinuation of IFX in four of them. Eleven patients developed a serious adverse event. Six patients needed hospitalization for an inflammatory event, one patient was diagnosed with refractory anaemia and three patients developed a malignancy. Finally, one patient committed suicide.

3.6. Short-term post-operative complications

Twenty-one patients underwent proctocolectomy with ileal pouch-anal anastomosis 3.3 (range 0.5–25.7) months after last infusion with IFX. Ten of them underwent surgery within 2 months of last IFX infusion.

We did not observe post-operative mortality. In none of the patients the pouch failed. Two patients developed a short-term post-operative complication. A 55-year old male, undergoing a proctocolectomy 1.3 months after IFX, developed a long-standing superficial wound infection. He was under concomitant therapy with corticosteroids and low dose oral cyclosporine and developed an anastomotic leak which was conservatively managed by rinsing. Prior to surgery he was under mesalazine and topical treatment with beclomethasone.

4. Discussion

The ACT1&2 trials clearly showed that IFX is efficacious for induction and maintenance of clinical remission in patients with moderate-to-severe UC. Despite compelling evidence for efficacy on the short-term, data on long-term outcome are lacking. In this trial 121 outpatients who received IFX for refractory colitis in a single centre were followed up for a median (IQR) of 33.0 (17.0–49.8) months. Sixty-eight percent of patients showing initial clinical response, had sustained clinical response during follow-up and 21 patients (17%) came to colectomy. Independent predictors of colectomy were absence of short-term clinical response, a baseline CRP ≥5 mg/L and previous IV treatment with corticosteroids and/or cyclosporine.

The main limitations of this study are its retrospective character and the use of a rather heterogeneous cohort including patients who took part in the ACT1 trial (n = 30). However, to approach a more everyday clinical practice, we also analysed the subgroup of 91 patients who received IFX for refractory UC outside ACT1. The findings on sustained clinical response and colectomy in this subgroup were almost identical to those in the overall cohort, and the same predictors were identified.

Although using other definitions, our data on short-term clinical response in the subgroup of 91 patients are similar to the data from the ACT1&2 trials (62% vs. 61–69%). Data on short-term mucosal healing (43% vs. 59–63%), however, cannot be compared directly, since endoscopy for evaluating response to IFX was only performed in 56% of our cohort. The real rate of mucosal healing in our cohort was probably higher than the reported 43% as, before the introduction of the Belgian reimbursement guidelines, we did not routinely perform endoscopy in patients who showed clinical improvement after administration of IFX.

From the 60 patients (66%) who achieved clinical response to IFX outside ACT1, 67% had a sustained clinical response. This figure seems somewhat higher than the data of the ACT1 trial (44–46%), probably due to the difference in definition of sustained clinical response. In the ACT1 trial the term sustained clinical response was reserved for patients who showed clinical response (based on Mayo score) at each time point (weeks 8, 30 and 54). In the literature, only one small trial looked for steroid-free remission beyond 1 year. In this British study including 30 patients with refractory UC, only 17% of patients who received episodical therapy with IFX achieved steroid-free remission after a median (range) follow-up of 13 (2–72) months.

During a median (IQR) follow-up of 33.0 (17.0–49.8) months, 17% of our 121 outpatients needed colectomy for refractory UC. This figure is considerably lower than the 53% in the British study, however the latter trial included patients with acute severe steroid-refractory colitis and no induction or
maintenance regimen was used. Absence of short-term clinical response, a baseline CRP $\geq 5$ mg/L and previous IV treatment with corticosteroids and/or cyclosporine were revealed as independent predictors of colectomy in our cohort. The previously reported predictive role of young age at diagnosis, could not be confirmed. The reported association with MDR1 C3435T and need for colectomy in univariate analysis, is probably due to the fact that patients with the TT genotype had a more severe colitis, suggested by the higher median dose of steroids at baseline.

Interestingly, we were not able to identify a beneficial role for the use of a maintenance regimen (IFX every 8 weeks) nor for the concomitant use of immunomodulators. Whether this is due to the uncontrolled design of our study or whether this illustrates a true lack of benefit is not clear. However, in contrast to compelling evidence in CD, no data is available on the role of maintenance IFX therapy and concomitant immunomodulators in UC.

Since mortality of UC in specialist units is currently no more than 1% including surgical mortality, an increased mortality resulting from drug therapy is unacceptable. In our cohort, we reported one patient who committed suicide, most likely not related to his therapy. We did, however, report six patients with a severe infectious adverse event within 2 months after a last infusion with IFX, and three patients who developed a malignancy. Whether these events can be attributed to IFX is not clear, since all these patients were under concomitant therapy with corticosteroids, methotrexate, azathioprine or 6-mercaptopurine.

Recently, the Mayo clinic reported a relatively high incidence (28%) of short-term post-operative infectious complications in 47 patients who underwent proctocolectomy after treatment with IFX. In our cohort only one out of 21 patients developed a long-standing superficial wound infection and one more patient was treated for an anastomotic leak.

In conclusion, our data support the use of IFX in outpatients with refractory UC, with 67% achieving clinical response and 68% of them showing sustained clinical response. During median follow-up of more than 2.5 years, 17% of patients needed colectomy. We were able to identify predictors of need for colectomy (absence of short-term clinical response, an elevated baseline CRP and previous IV treatment with corticosteroids and/or cyclosporine), but these still need confirmation in a prospective trial. The risk of post-operative complications was not increased. However, the occurrence of serious infections and malignancies accentuates the need for extensive alertness to adverse events.

Conflict of interest

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