

CLINICAL-ALIMENTARY TRACT

Withdrawal of Immunosuppression in Crohn's Disease Treated With Scheduled Infliximab Maintenance: A Randomized Trial

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See Peyrin-Biroulet P et al on page 644 and Gardiner SJ on page 654 in *CGH*; See editorial on page 2161.

Background & Aims: The benefit to risk ratio of concomitant immunosuppressives with scheduled infliximab (IFX) maintenance therapy for Crohn's disease is an issue of debate. We aimed to study the influence of immunosuppressives discontinuation in patients in remission with combination therapy in an open-label, randomized, controlled trial.

Methods: Patients with controlled disease ≥ 6 months after the start of IFX (5 mg/kg intravenously) combined with immunosuppressives were randomized to continue (Con) or to interrupt (Dis) immunosuppressives, while all patients received scheduled IFX maintenance therapy for 104 weeks. Primary end point was the proportion of patients who required a decrease in IFX dosing interval or stopped IFX therapy. Secondary end points included IFX trough levels, safety, and mucosal healing. **Results:** A similar proportion (24/40, 60% Con) and (22/40, 55% Dis) of patients needed a change in IFX dosing interval or stopped IFX therapy (11/40 Con, 9/40 Dis). C-reactive protein (CRP) was higher and IFX trough levels were lower in the Dis group (Dis: CRP, 2.8 mg/L; interquartile range [IQR], 1.0–8.0; Con: CRP, 1.6 mg/L; IQR, 1.0–5.6, $P < .005$; trough IFX: Dis: 1.65 $\mu\text{g/mL}$; IQR, 0.54–3.68; Con: 2.87 $\mu\text{g/mL}$; IQR, 1.35–4.72, $P < .0001$). Low IFX trough levels correlated with increased CRP and clinical score. Mucosal ulcers were absent at week 104 in 64% (Con) and 61% (Dis) of evaluated patients with ongoing response to IFX. **Conclusions:** Continuation of immunosuppressives beyond 6 months offers no clear benefit over scheduled IFX monotherapy but is associated with higher median IFX trough and decreased CRP levels. The impact of these observations on long-term outcomes needs to be explored further.

The chimeric monoclonal antitumor necrosis factor (TNF) antibody, infliximab (IFX), has proven to be an efficacious therapy for refractory luminal and fistulizing Crohn's disease (CD) and more recently for refractory ulcerative colitis.¹⁻⁵ In CD, initial retrospective cohort studies have suggested that efficacy of IFX short-term is superior in patients treated with concomitant immunosuppression.⁶⁻¹⁰ Concomitant immunosuppression is considered to protect mainly against immunogenicity induced by IFX. When used in an episodic, on-flare, regimen, IFX is likely to induce antibodies to infliximab (ATI) leading to infusion reactions and to shorter duration of response.⁹⁻¹³ Nevertheless, in clinical practice, episodic retreatment with variable intervals and systematic maintenance strategies are currently in use. Systematic 8-weekly maintenance therapy with IFX 5 mg/kg intravenously (IV) is associated with decreased formation of ATI and appears to be the optimal strategy to minimize the immunogenicity of IFX. This observation suggests that continuous exposure tolerizes the human body to a chimeric (human-mouse) antibody such as IFX. In patients treated with IFX on a scheduled maintenance basis, concomitant immunosuppressive therapy is not clearly associated with increased efficacy. Furthermore, a significant impact of concomitant immunosuppressives on the incidence of ATI formation was not observed, although none of the studies was powered to test for differences in immunogenicity.^{11,12} In addition, preliminary data indicate that the combination of immunosuppressive therapies in patients with inflammatory bowel disease (IBD) increases the likelihood of adverse events including serious infections and

Abbreviations used in this paper: ATI, antibodies to infliximab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Diseases Questionnaire; IFX, infliximab; IQR, interquartile range; IV, intravenously; SC, subcutaneous; SES-CD, simple endoscopic score-Crohn's disease; TNF, tumor necrosis factor.

cancer.¹⁴ Alternatively, in patients with rheumatoid arthritis, methotrexate and anti-TNF antibody cotherapy compared with anti-TNF monotherapy is not associated with an increased lymphoma risk.¹⁵ Recently, 11 cases of hepatosplenic T-cell lymphoma reported in young patients with IBD treated with IFX and azathioprine in combination therapy have heightened concerns about the safety of combined immunosuppressive treatment.¹⁶

The principal aim of the present study was to evaluate whether continuing standard immunosuppressives in patients who had been responding to a combination of IFX and immunosuppressives for at least 6 months adds to the long-term efficacy of scheduled maintenance as compared with IFX monotherapy. The study was designed as a multicenter, prospective, randomized, open-label, superiority trial.

Patients and Methods

Study Design

All patients ages 16 years or older and having received IFX in an episodic or systematic maintenance schedule were eligible if they had been treated with a combination of IFX 5 mg/kg IV dosed with intervals of 8 weeks or longer and an appropriate dose of immunosuppressives (azathioprine/6-mercaptopurine or methotrexate) for at least 6 months and provided they met all other inclusion criteria and none of the exclusion criteria. Appropriate dose of immunosuppressives was defined for azathioprine as a maintenance dose of 2–2.5 mg/kg/day or the maximally tolerated dose, for 6-mercaptopurine as a maintenance dose of 1.5 mg/kg/day or the maximally tolerated dose, and for methotrexate as a maintenance dose of 15 mg per week or the maximally tolerated dose. Compliance with azathioprine and 6-mercaptopurine therapy was assessed by questioning patients at each visit on the number of tablets taken daily and by following mean corpuscular volume. For subcutaneous (SC) methotrexate, all prescriptions were filled at the hospital pharmacy. Additional inclusion criteria were documented full clinical response to IFX and disease control at entry into the trial and IFX therapy initiated for signs and symptoms of luminal CD. Disease control was defined as the absence of intestinal or extraintestinal symptom as judged by both patient and physician. Exclusion criteria were previous infusion reactions related to IFX and not controlled with prophylactic treatment, pregnancy and lactation, intercurrent medical conditions precluding further IFX or immunosuppressive therapy, imminent need for CD-related surgery, abdominal enterocutaneous fistula or actively draining perianal fistula, and infectious causes of diarrhea. After confirmation of eligibility, patients were randomized 1:1 to receive either IFX (5 mg/kg IV) scheduled 8 weekly retreatment from week 0 until week 104 with continuation of immunosuppressives at the same dose (Con) or IFX 5 mg/kg IV 8 weekly with discontinuation

at baseline of concomitant immunosuppressives (Dis). Systemic steroids or oral budesonide and rectal steroids or mesalamine were not allowed. Oral aminosalicylates were kept stable during the trial. The protocol was approved by the University of Leuven Ethics Committee for Clinical Trials, and written informed consent was obtained from all patients.

Study Evaluations and End Points

Patients received 8-weekly treatments with IFX (5 mg/kg). Blood samples were collected before every infusion with recordings of Crohn's Disease Activity Index (CDAI)¹⁷ and Inflammatory Bowel Diseases Questionnaire (IBDQ),¹⁸ and physical examination were performed. In addition, occurrence of a disease flare, serious adverse events, infusion reactions and delayed hypersensitivity reactions, intercurrent surgery, or procedures and/or rescue treatment was recorded every 8 weeks. Every 16 weeks, all adverse events were noted in addition. Serum samples were obtained prior to each infusion for measurement of IFX "trough" levels and ATIs. Infliximab serum concentrations were measured as previously published with an enzyme-linked immunosorbent assay (ELISA) using TNF preincubated microplates and an anti-human IgG indicator antibody.¹⁹ Serum concentrations of ATI were analyzed using a double-antigen ELISA based on their capture by IFX-coated microplates and their detection by peroxidase-coupled IFX. Because of the interference of circulating infliximab, results were conclusive if IFX concentration was $<1.7 \mu\text{g/mL}$. In case of a CD flare, prior to the next scheduled infusion, the dosing interval was shortened by 2 weeks. Increasing the IFX dose to 10 mg/kg was not allowed. An increase of the CDAI to at least 70 points above the baseline value was defined as a luminal disease flare. Endoscopic severity was assessed with the simple endoscopic score–Crohn's disease (SES-CD) score (range, 0–56), which incorporates size of ulcers and ulcerated area, affected area, and stenosis.²⁰ Also, factors at baseline (sex, time to start of IFX, previous on-demand IFX treatment schedule, disease location, type of immunosuppressive, and smoking status) were evaluated for prediction of failure. Infusion reactions were managed adhering to local standing orders and at the discretion of the treating physician. Prophylactic treatment for patients with documented infusion-related reactions was tailored to the severity of the reactions. IV corticosteroids (maximum, 250 mg hydrocortisone or equivalent) and oral or parenteral antihistaminics were allowed. This prophylaxis was kept stable while the patient was on the trial.

Data Analysis

Baseline patient characteristics were explored with descriptive statistics. The primary end point of this trial was the proportion of patients needing early rescue IFX because of a disease flare or interrupting further IFX

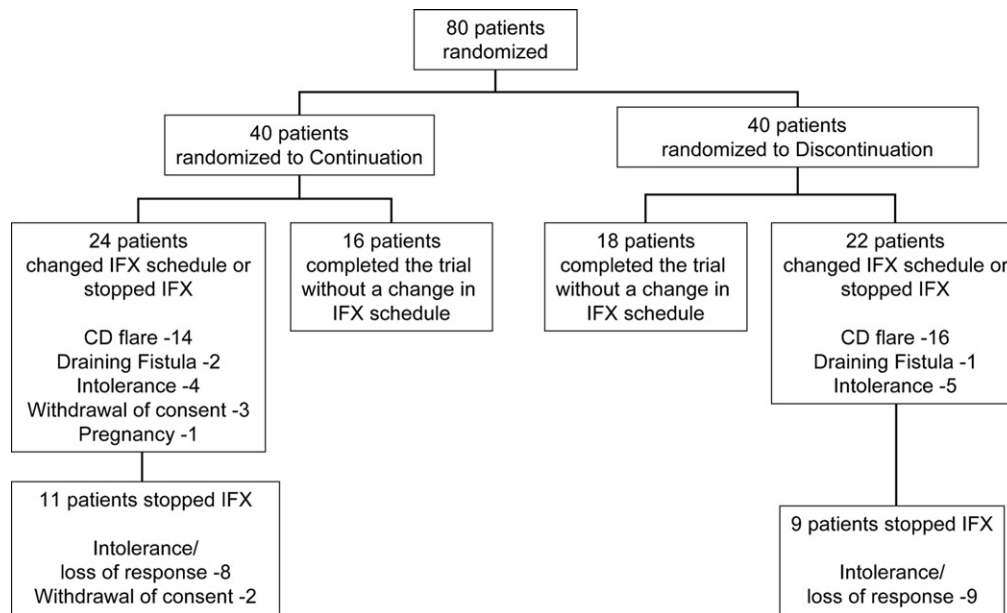


Figure 1. Patient disposition throughout the trial. Patients achieving the primary end point of needing a change in IFX dosing schedule, including stopping IFX dosing, are represented first. Patients who stopped further infliximab dosing are also listed separately.

dosing because of loss of response, intolerance, or intercurrent adverse event. Secondary end points included the proportion of patients interrupting further IFX dosing, endoscopic mucosal healing at week 104, safety and tolerability of IFX in each arm, serum IFX trough levels, and immunogenicity (defined as presence of ATIs). Randomization on a 1:1 basis without stratification was centralized at the University of Leuven hospitals. Data were analyzed on an intention-to-treat basis using SPSS 15.0 software (SPSS, Inc, Chicago, IL). Two-tailed Fisher exact tests were used to test for difference between proportions and Kruskal-Wallis and Mann-Whitney tests for non-parametric observations. Univariate analysis was used to test for predictive values with Bonferroni correction for multiple comparisons. Kaplan-Meier analysis with log-rank statistics was performed to test for differences in time to failure and time to interruption of IFX. Patients who achieved the primary end point (needing an interval change or stopping IFX therapy) were censored at that

time, and CRP, CDAI, and IFX trough levels were not collected afterwards, although these patients were still followed for safety and loss of response. In the intention-to-treat analysis, the last observation carried forward was used for CRP, CDAI, and IFX trough levels. The study was designed as a superiority trial to detect a clinically relevant difference of 35% between the 2 groups with a power of 80% assuming that 25% of patients in the immunosuppressives continuation group would achieve the primary end point over the study period of 104 weeks. The power to detect a 10% difference was 10%. Statistical significance was accepted at the 5% level.

Results

Patient Demographics

Forty patients were included and randomized in each arm between February 2004 and May 2005 (Figure 1). As shown in Table 1, there were no differences be-

Table 1. Patient Demographics

	Continuation group	Discontinuation group	P value
Number	40	40	
Age, y	35.6 ± 9.5	35.4 ± 10.8	.76
Sex	42.5% Male	47.5% Male	.45
Duration of disease, median (range), y	9 (1–36)	9 (2–25)	.86
Baseline CDAI	137.6 ± 90.1	138.1 ± 98.7	.98
Baseline CRP, median (IQR), mg/L	3.4 (1.0–10.6)	3.2 (1.0–7.1)	.54
Location (% colonic only)	32.5%	12.5%	.16
Active smokers	45.0%	47.5%	.82
Previous on-demand/scheduled every 9–12 weeks/scheduled every 8 weeks treatment	33%/15%/52%	38%/12%/50%	.80
Time since start IFX, median (range), mo	34.5 (6–112)	24.5 (6–90)	.73
Time since start immunosuppressives, median (range), mo	37 (6–112)	25 (6–98)	
Weight, kg	69.8 ± 13.7	71.2 ± 19.7	.76

NOTE. All parameters not significantly different.

Table 2. Adverse Events and Serious Adverse Events

	Continuation group	Discontinuation group
Serious AEs	3/40 (7.5%)	3/40 (7.5%)
	1 Pregnancy	1 Appendectomy
	1 Pneumonia	1 Skin carcinoma
	1 Partial colectomy	1 Ureterolithiasis
AEs		
Patients with ≥ 1 AE	60%	62.5%
Total number of AEs	60	42
Infections	12	10
Liver test elevations	2	0
Arthralgias/arthritis	9	8
Infusion reactions	3	2

NOTE. In the safety follow-up of this trial, we recorded 1 renal cell carcinoma (Con group) and 1 sudden cardiac death (Dis group). Both patients had discontinued IFX for more than 8 weeks. AE, adverse event.

tween the groups for age, sex, smoking status, weight, duration of disease, baseline CDAI and CRP, disease location, duration of IFX or immunosuppressives therapy, type of immunosuppressive, and previous IFX maintenance strategy (Table 1). None of the patients had received a loading scheme with IFX 5 mg/kg at 0, 2, and 6 weeks because this strategy is not used in patients with CD at our centers. Patients with on-demand therapy, systematic 9- to 12-week, and systematic 8-week maintenance, were evenly distributed.

Clinical Outcomes

Twenty-four out of 40 (60%, 95% CI: 45%–74%) patients in the continuation and 22 of 40 (55%, 95% CI: 40%–69%; difference between groups, 5%; 95% CI: 0.50%–17%) in the discontinuation group needed a change in the IFX dosing schedule or stopped IFX dosing ($P = .65$), which was the primary end point. The main reason for

shortening the dosing interval was CD flare (Con: 14/24 patients; Dis: 16/22 patients; Figure 1). Infliximab dosing was definitively stopped in 11 (27%, 95% CI: 16%–43%) patients (Con) and 9 (22%, 95% CI: 12%–38%) patients (Dis) (between group difference, 5%; 95% CI: 0.50%–17%), respectively, and predominantly for loss of response and/or intolerance (Con: 8/11 patients, Dis: 9/9 patients; Table 2). Kaplan–Meier analysis indicated that the time to shortening of the interval between IFX infusions or time to stopping IFX dosing was not different between the 2 groups (log rank: $P = .74$ [interval change] and $P = .35$ [stop IFX]; Figure 2). Median CDAI and IBDQ were not different between the 2 groups from week 8 through week 104 (CDAI median and interquartile ranges [IQR]: Con: 92 [34–164], Dis: 104 [55–165]; IBDQ median [IQR]: Con: 174 [157–196], Dis: 176 [158–194]) Adverse events were evenly distributed. In total, 60% of patients in the continuation and 62% in the discontinuation group reported side effects, and serious adverse events were noted in 3 patients in both groups (Table 2). The mortality rate in the trial was 0%, and the malignancy rate was 1.2% (1/80, basocellular skin Ca, discontinuation group). Two additional serious adverse events, a renal cell carcinoma (Con) and a sudden cardiac death (Dis), were observed within the study period of 104 weeks, both in patients who had discontinued IFX for more than 8 weeks prior to the event because of loss of response. Predefined potential predictors of failure were tested in univariate analysis. Sex, time to start of IFX, previous on-demand IFX treatment schedule, disease location, type of immunosuppressive, previous allergic reaction, and smoking status were not associated with poor outcome (Table 3), and a multivariate analysis was not performed. In addition, when patients were stratified based on prior IFX dosing strategy in a post hoc analysis, we observed no difference in clinical outcomes, CRP, IFX

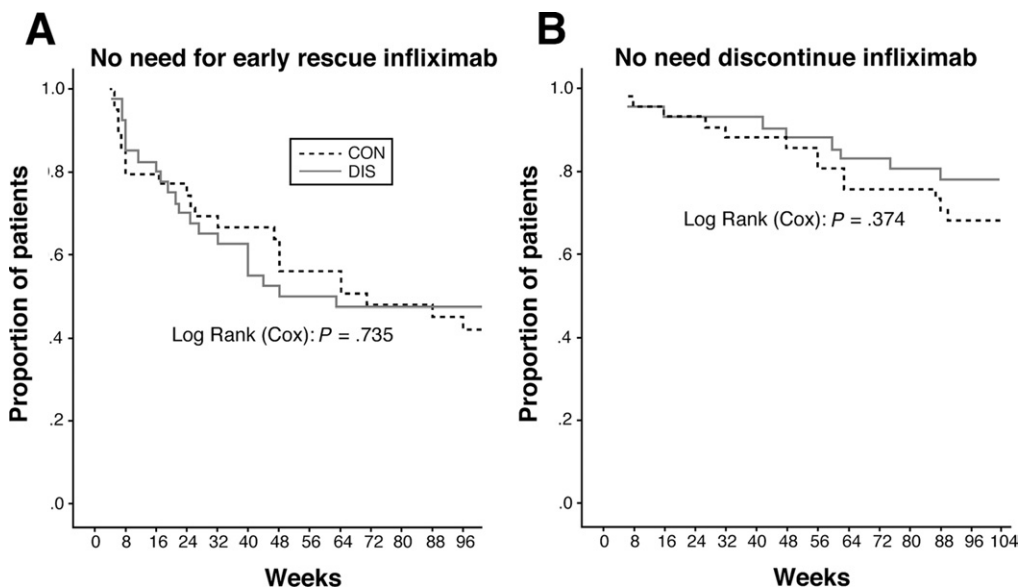


Figure 2. Life table analysis (Kaplan–Meier) of the patient outcomes. (A) Analysis in both groups of the need for early-rescue IFX or stopping IFX therapy (primary end point). (B) Analysis in both groups of the need to stop further IFX therapy. P values are listed for the log-rank test only.

Table 3. Factors Evaluated as Potential Predictors of the Need of a Change in IFX Dosing Interval and the Need to Discontinue IFX Therapy

	Need for early rescue IFX (n = 46)		Need to discontinue IFX (n = 20)	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex, male (36/80)	0.58 (0.24–1.41)	.26	2.38 (0.72–7.88)	.35
Immunosuppressive MTX (26/80)	0.52 (0.20–1.35)	.23	1.69 (0.57–5.50)	.39
Previous reaction (14/80)	0.28 (0.08–1.01)	.17	0.78 (0.69–0.89)	.06
Previous on-demand treatment (28/80)	0.96 (0.38–2.46)	.93	0.41 (0.13–1.40)	.14
Ileal or ileocolonic disease (62/80)	0.74 (0.28–1.95)	.37	1.11 (0.31–3.97)	.87
Nonsmoker (43/80)	2.13 (0.87–5.25)	.12	1.71 (0.58–5.78)	.35

NOTE. P = corrected P value for multiple comparison (Bonferroni).

trough levels, or CDAI for patients with prior on-demand (>12 weeks interval), scheduled every 9–12 weeks, or scheduled every 8 weeks interval treatment.

Biologic End Points

Median CRP level at baseline was not different between the 2 groups (Table 1). Fourteen of 40 (Con) and 12 of 40 (Dis) patients had an elevated CRP (>5 mg/L) level at baseline. Eight of 16 patients (50%) who experienced a flare and needed early rescue IFX (primary end point) had an elevated CRP level in the Dis group as compared with 9 of 14 (64%, NS) in the Con group. Overall, the CRP levels from week 8 through week 104

were significantly higher in the Dis group (median, 2.8; IQR, 1.0–8.0) than in the Con group (median, 1.6; IQR, 1.0–5.6, P < .005). At most individual time points, median CRP values were numerically higher in the Dis group, but the differences did not reach significance (Figure 3). Baseline IFX serum trough levels were similar in both groups, although a high interpatient variability was observed (Figure 4). Last observation carried forward (IFX level at the primary end point) was used to compensate for missing trough levels in patients with a change in their dosing interval. The median trough levels from week 8 through week 54 were significantly higher in the Con group than in the Dis group (median [IQR]:

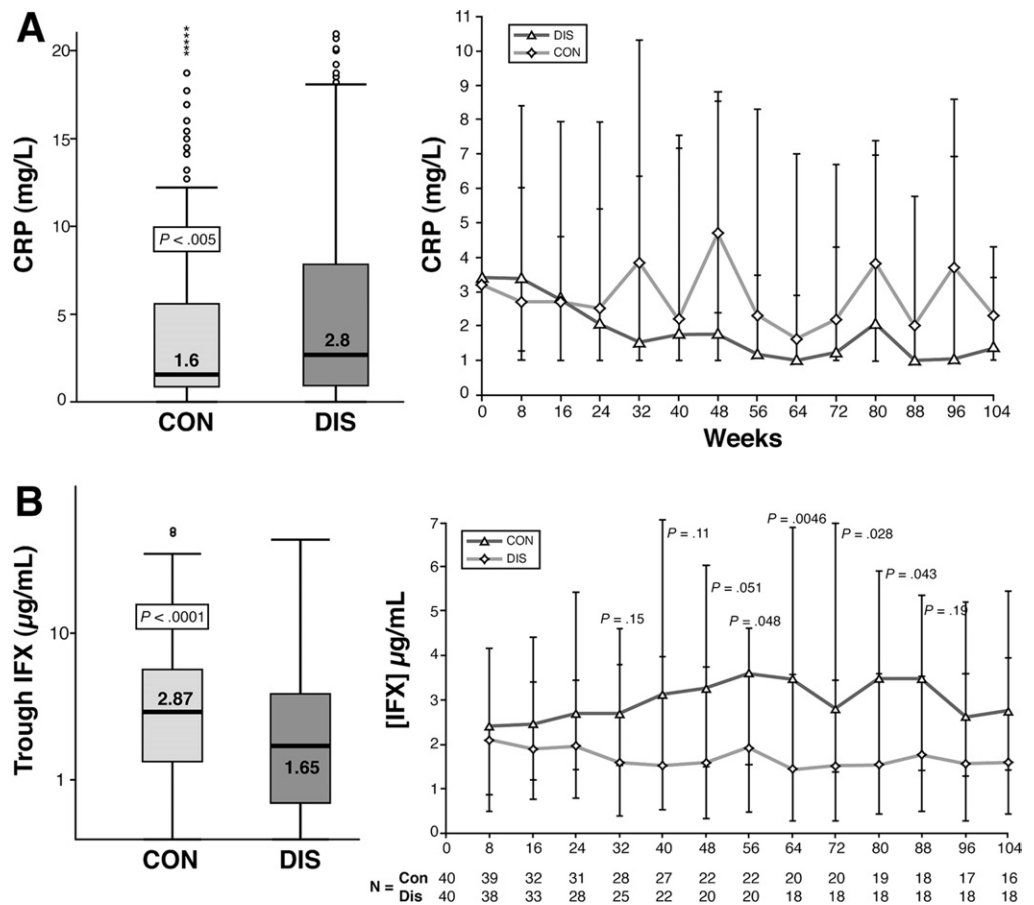


Figure 3. CRP (A) and IFX trough levels (B) in both groups throughout the trial. In the graphs with individual time points, data are represented as medians and IQR. The dotted line in panel A marks the upper limit of normal for CRP (5 mg/L). Levels of significance are indicated when appropriate. Numbers below the x-axis in panel B represent the number of patients still on the trial, who had not achieved the primary end point.

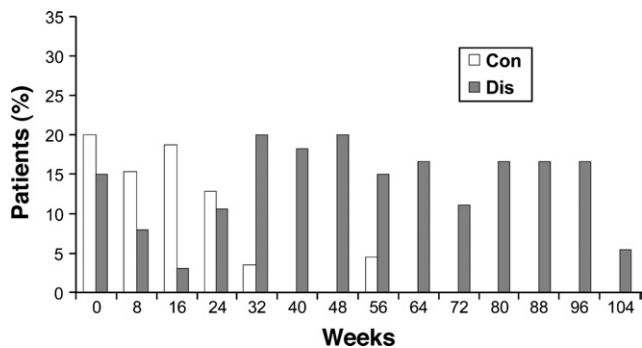


Figure 4. Proportion of patients with undetectable IFX trough serum levels in both arms and at different time points throughout the trial. Data are expressed as percentage of patients still on the trial (for patient numbers see Figure 3B).

Con: 2.87 [1.42–4.80] $\mu\text{g/mL}$, Dis: 1.65 [0.54–3.53] $\mu\text{g/mL}$, $P < .0001$. At individual time points, significantly lower levels were observed from week 40 through week 88. At later time points, more patients had undetectable IFX trough serum levels in the Dis group (Figure 4). ATIs were infrequently found (Con: 5.0% [2/40], Dis: 12.5% [5/40], $P = .43$). Also in patients with low IFX trough levels at repeated time points allowing for conclusive assessment ($<1.7 \mu\text{g/mL}$, 39/80), only 18% were ATI positive.

Overall CRP and CDAI values correlated with IFX trough levels (CRP: $r = 0.387$, CDAI: $r = 0.205$, $P < .01$). In an exploratory analysis, we categorized all CRP and CDAI values with a matching IFX serum level depending on the corresponding trough levels in 4 groups based on the quartiles of the trough levels (Q1, 0–25th percentile: 0–0.90 $\mu\text{g/mL}$; Q2, 25th–50th percentile: 0.91–2.23 $\mu\text{g/mL}$; Q3, 50th–75th percentile: 2.24–4.54 $\mu\text{g/mL}$; Q4, 75th–100th percentile: $\geq 4.55 \mu\text{g/mL}$.) Low trough levels were associated with higher median levels of CRP in Q1

and Q2 ($P < .0001$) and in Q1 for CDAI ($P < .05$) (Figure 5). Low or undetectable trough levels (Q1 and Q2, 0–2.23 $\mu\text{g/mL}$) at week 8 were also associated with a higher proportion of patients needing a change in IFX dosing interval (69.4% [Q1–Q2] vs 42.9% [Q3–Q4], $P < .01$; odds ratio (OR), 3.99 [95% CI: 1.53–10.11]).

Endoscopic End Point

Ileo-colonoscopy was performed in 49 of 60 patients with ongoing IFX therapy, including those with a change in dosing interval (10/60 patients declined colonoscopy, 1/60 had no colonic lesions before starting IFX). Endoscopic healing with absence of mucosal ulcers was observed in 16 of 25 (64%, Con) and 14 of 23 (61%, Dis) and aphtous ulcers ($<0.5 \text{ cm}$) or no ulcers in 80% and 87% of patients, respectively. Information on mucosal lesions before starting IFX was available in 31 of these 49 patients, and all 31 patients had ulcers at that time. Median SES-CD endoscopic severity scores in patients with ongoing IFX therapy were 1 (Con: range, 0–14) and 2.5 (Dis: range, 0–13, NS), respectively. CRP levels correlated with endoscopic severity scores ($r^2 = 0.202$, $P = .01$).

Discussion

The benefit of conventional immunosuppressives such as thiopurines and methotrexate in combination with scheduled IFX maintenance therapy is still debated. In this study, we aimed to investigate the additional benefit of immunosuppressives continuation in patients with luminal CD treated with scheduled IFX maintenance beyond the induction period. We found no advantage of continuing immunosuppressives for clinical outcomes including mucosal healing. However, the combined treatment approach resulted in sustained high IFX trough levels and lower CRP values. In addition, the

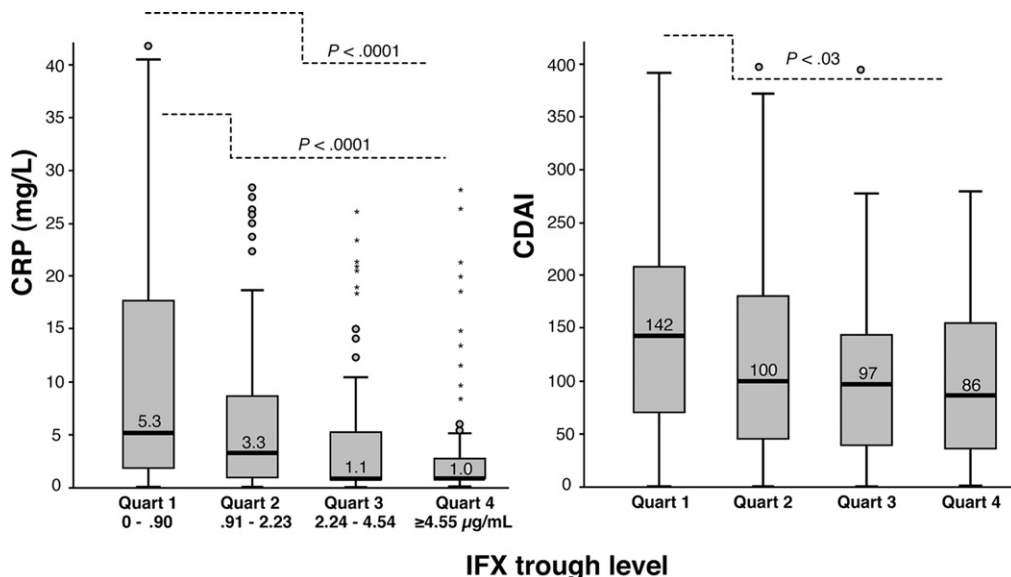


Figure 5. CRP levels and CDAI scores in all patients measured at all study time points expressed as a function of trough serum IFX levels ($\mu\text{g/mL}$). Trough levels below 0.3 $\mu\text{g/mL}$ and below 2 $\mu\text{g/mL}$ were associated with elevated median CRP levels. CDAI was not affected by trough IFX levels.

results clearly indicate that sustained clinical response to IFX is accompanied by mucosal healing after a time period of 2 years. Our results confirm the data from IFX induction trials²¹ and from ACCENT I²² in that we show durable mucosal healing at 2 years in patients with ongoing clinical response to infliximab maintenance therapy.

Several retrospective observations have indicated that concomitant immunosuppressives at onset of IFX therapy are associated with improved short-term benefit and result in better long-term clinical outcomes when episodic therapy is used by decreasing the immunogenicity of this chimeric monoclonal antibody.⁸⁻¹³ However, with systematic IFX maintenance therapy, a protective effect of immunosuppressives has not been clearly demonstrated, although no study has been prospectively powered to specifically address this question.^{11,12} In the current trial, all patients had been treated with IFX and immunosuppressives in combination for at least 6 months. When IFX is dosed with intervals of more than 8 weeks duration, there is theoretically an increased risk of immunogenicity and secondary loss of response, but we did not observe a difference in clinical or biologic end points for patients with prior IFX dosing intervals of >12 weeks, 9-12 weeks, or 8 weeks, respectively. Although, clearly, over a period of 2 years more than 50% of the patients needed an adjustment in their dosing schedule, less than 25% stopped IFX therapy because of intolerance and/or loss of response. This was an open-label trial, and we followed a "real life" approach. The decision to shorten the dosing interval was mainly based on disease symptoms (CDAI driven) and not on endoscopic criteria nor on an increase in CRP. The open-label nature may have introduced several biases specifically toward overreporting of disease flares in patients who discontinued immunosuppressives. Although all previous controlled trials with IFX have been exclusively guided by CDAI, our approach may partially explain why up to 50% of patients with a symptomatic CD flare had no increased CRP. In this respect, it is important to note that there was also no difference between the 2 groups in proportion of IFX therapy patients stopping because of loss of response.

This study is mainly limited by the fact that we assumed "superiority" of continued immunosuppressives, and it was not powered to detect subtle differences in clinical benefit between the 2 strategies. To ascertain the equivalence of both strategies, an adequately powered noninferiority trial with 250 or more patients in each arm would be required. Therefore, we may have missed a smaller increase in the proportion of patients losing the efficacy of IFX after discontinuation of immunosuppressives. However, at no time during the 104 weeks follow-up could a trend toward more or earlier relapse in the discontinuation group be inferred from the life table analyses. Also, no prospective trials, which could be used as a reference to estimate the risk difference, have been published.

Interestingly, in this study, stopping immunosuppressives after at least 6 months of combined therapy with IFX resulted in a gradual decrease of serum IFX trough levels over time. The influence of withdrawing immunosuppressives on the pharmacokinetics of infliximab had no major impact on the clinical response over a 2-year time period, but we found higher overall CRP levels in the group with discontinuation of immunosuppressives. In addition, undetectable or low IFX trough levels were associated with increased CRP and with a higher need for a change in dosing interval. We, therefore, confirm an earlier observation in a cohort of patients with CD treated with scheduled or episodic IFX maintenance of a clear association between trough serum IFX and CRP levels and also the association of a continuous decay in trough serum IFX below 2 $\mu\text{g}/\text{mL}$ with loss of endoscopic and clinical remission.¹² The increased CRP levels may reflect a state of "subclinical inflammation" because they also correlated with endoscopic severity. On the contrary, patients with normalization of CRP levels, endoscopic healing, and high sustained IFX trough levels are probably in definitive remission as far as the inflammatory reaction is concerned. Whether this "clinical and biological remission" impacts on the disease course beyond 2 years of follow-up needs to be explored further. It is unclear whether these differences in CRP and IFX trough levels herald an increased loss of response over time. If this were true, it may negatively impact on patient outcomes because a recent controlled trial with another anti-TNF antibody, adalimumab, indicated that patients with prior loss of response or intolerance to IFX are less likely to respond to a second anti-TNF antibody.

In contrast to earlier observations of an association between antibodies to infliximab (ATIs) and IFX trough levels with episodic infliximab retreatment therapy,^{9,13} we were unable to identify a clear influence of ATI formation on the pharmacokinetics of scheduled IFX retreatment. However, the interference of IFX serum levels with the ATI assay precludes firm conclusions about the degree of immunogenicity in both groups, particularly considering the observed differences in IFX trough levels. Alternatively, immunosuppressives could impact on the pharmacokinetics of IFX via other pathways than the prevention of ATIs. In CD, there are no prior prospective studies on the impact of concomitant immunosuppressive therapy on pharmacokinetics of scheduled infliximab retreatment. In patients with rheumatoid arthritis, a high interindividual variability in IFX trough levels had previously been shown in agreement with our results.²³ As a rescue strategy for early CD flares during maintenance IFX therapy, we shortened the interval between infusions rather than increasing the dose per infusion, a strategy that was confirmed to result in higher sustained IFX levels than increasing the dose.²⁴

In conclusion, in this prospective trial, continued combined IFX and immunosuppressive treatment beyond 6

months was not superior to withdrawal of immunosuppressives despite higher IFX concentrations and lower CRP levels with combination therapy. Scheduled IFX maintenance therapy combined with immunosuppressives and scheduled IFX monotherapy are 2 alternative strategies trading the risk of losing efficacy for a possible gain in long-term safety. Our observation of changes in IFX pharmacokinetics and in a biomarker of inflammation after discontinuation of immunosuppressives may precede loss of efficacy in a proportion of patients and should be explored in larger prospective trials.

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