Early Trough Levels and Antibodies to Infliximab Predict Safety and Success of Reinitiation of Infliximab Therapy

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This article has an accompanying continuing medical education activity on page e91. Learning Objectives—At the end of this activity, the successful learner will be able to identify clinical and biological factors predictive of safe and successful restarting of infliximab after a drug holiday. This will translate in a safe and more effective (re)start of infliximab, especially in patients at high risk.

BACKGROUND & AIMS: **Few agents are available for the treatment of inflammatory bowel diseases, and patients frequently become unresponsive to biologics. We investigated the feasibility of reinitiating infliximab therapy for patients who previously received only episodic therapy with, lost response to, or had infusion reactions to infliximab. We also aimed to identify factors associated with the success and safety of restarting infliximab, such as antibodies to infliximab and trough levels of the drug.**

METHODS: **From the inflammatory bowel disease biobank, we identified 128 consecutive patients (105 patients with Crohn's disease, 23 patients with ulcerative colitis) who restarted infliximab after a median 15-month discontinuation (range, 6–125 mo; 28 patients for loss of response or infusion reactions, 100 patients for remission or pregnancy). We also analyzed serum samples that had been collected during the first period of infliximab therapy (T-1), when therapy was reinitiated (T0), and at later time points (T+1, T+2) for trough levels and antibodies to infliximab. We investigated correlations among response to treatment, infusion reactions, treatment modalities, trough levels, and antibodies to infliximab.**

RESULTS: **Reinitiation of infliximab therapy produced a response in 84.5% of patients at week 14, 70% of patients at 1 year, and in 61% of patients at more than 4 years. Fifteen patients had acute infusion reactions and 10 patients had delayed infusion reactions. The absence of antibodies to infliximab at T+1 (hazard ratio [HR], 0.14; 95% confidence interval [CI], 0.026–0.74; $P = .021$) and reinitiation with concomitant immunomodulator therapy were associated with short-term responses (HR, 6.0; 95% CI, 1.3–27; $P = .019$). Pregnancy or remission as reason for discontinuation (HR, 2.70; 95% CI, 1.09–6.67; $P = .033$) and higher trough levels at T+1 (HR, 2.94; 95% CI, 1.18–7.69; $P = .021$) were associated with long-term response. Undetectable antibodies to infliximab at T+1 were associated with the safety of reinitiating therapy (HR for infusion reaction with detectable antibodies to infliximab, 7.7; 95% CI, 1.88–31.3; $P = .004$).**

CONCLUSIONS: **Reinitiating infliximab therapy can be safe and effective for patients with Crohn's disease or ulcerative colitis after a median 15-month discontinuation period.**

Keywords: Remicade; Drug Holiday; Antidrug Antibody; Pharmacokinetics.

See editorial on page 1482.

Current recommendations are to continue anti–tumor necrosis factor (TNF) as a regularly scheduled maintenance therapy when patients have a complete or good partial response upon the initial induction treatment.[1] Despite this standard maintenance therapy, a significant group of patients who initially

Abbreviations used in this paper: **ATI, antibodies to infliximab; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, infliximab; IMM, immunomodulator; IR, infusion reaction; IV, intravenous; LOR, loss of response; ROC, receiver operating curve; TL, trough level; TNF, tumor necrosis factor.**

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respond have a loss of response (LOR) over time.[2–5] A large body of evidence has emerged showing that immunogenicity (ie, the generation of antidrug antibodies) at least partially explains this LOR. Trough level (TL) measurements and the detection of antidrug antibodies are new diagnostic tools to asses pharmacokinetics, including immunogenicity, and potentially improve the durable efficacy and safety of anti-TNF therapy.[6]

Apart from LOR and despite the current recommendations patients sometimes will discontinue therapy for various reasons including durable remission, pregnancy, safety, or financial concerns. When symptoms reappear, restarting anti-TNF can be indicated. Very little is known, however, about restarting the same anti-TNF agent after a drug holiday. Physicians often preemptively will switch from one anti-TNF agent to another when considering that patients might have developed antidrug antibodies during the previous course or will develop them after restarting treatment. Moreover, restarting an anti-TNF agent that was discontinued because of persistent LOR or the occurrence of an infusion reaction (IR) is considered not very useful and/or a major risk for an IR.

In this cohort we studied patients who restarted infliximab (IFX) for various reasons including LOR and IR. In addition, a proportion of patients was treated episodically during their first IFX course. Restarting IFX in these patients carries a high risk for developing antidrug antibodies and hence IRs and no response or secondary LOR.[7]

The aim of this study was to examine the safety and success of restarting IFX after a long drug holiday. Co-primary end points were to identify the role of IFX TLs and antibodies to IFX (ATI) and to find predictors of success and safety upon restarting IFX.

Materials and Methods

Study Design

This was a retrospective single-center study of a consecutive series of inflammatory bowel disease (IBD) patients followed up at the University Hospitals Leuven in Belgium.

Study Population

Through a systematic search of the IBD biobank we identified 132 patients (109 patients with Crohn's disease, 23 patients with ulcerative colitis) who had received IFX treatment in the past and who were restarted on IFX maintenance therapy after a minimum drug holiday of 6 months. Four patients were excluded from the series because of insufficient clinical data. Complete clinical information on treatment modalities and short-term and long-term treatment success and serial serum samples were available for 128 of 132 patients (97%). All but 1 patient had a minimum follow-up period of 1 year at the time of the last data analysis. All patients were retreated with IFX using maintenance therapy. However, the treatment modality of the first IFX course varied: 70 patients were treated episodically only during the first course, 16 patients were treated episodically initially and received maintenance treatment later, and 72 patients received maintenance treatment from the beginning. All patients were treated according to the Belgian reimbursement criteria for IFX. This means that all patients were allergic or refractory to steroids and/or immunomodulators (IMMs) (ie, azathioprine, 6 mercaptopurine, or methotrexate) for a minimum of 3 months before IFX was started. Only 5-mg/kg infusions were used. The treating physicians were not aware of TL and ATI measurements at the time of treatment decisions.

Data Collection

Clinical information on treatment modalities was collected retrospectively from the electronic patient charts. In addition to simple demographic data, the following data were collected in detail: for the first treatment period the start date of IFX, for episodic treatment the numbers of infusions, and for maintenance treatment the duration of IFX treatment. Treatment modalities were as follows: premedication with 250 mg intravenous (IV) hydrocortisone and 10 mg of levocetirizine orally at (re)start of IFX, a 3-dose (weeks 0, 2, and 6) induction regimen or not, the use of concomitant IMM co-treatment at the start of IFX, the reason for stopping the first IFX course (remission/pregnancy vs LOR despite dose intensification and/or shortening of the interval [LOR] and/or serious IR), and, finally, the duration of the drug holiday in months.

For the second treatment period the following data were collected: the start date and the duration of IFX maintenance treatment. Treatment modalities were as follows: IV steroid prophylaxis at initiation of IFX, single vs 3-dose (weeks 0, 2, and 6) induction dose, and the use of concomitant IMM at restart of IFX.

The co-primary end points were response to IFX retreatment and safety after restarting IFX.

The initial response to IFX was assessed by experienced clinicians (and retrospectively reconfirmed by the first author [F.B.]) at weeks 10 to 14. Patients who became completely symptom free were considered full responders to the IFX treatment. Patients who had distinct clinical improvement with an obvious decrease of disease activity (assessed by a standard clinical evaluation using clinical criteria, as included in the Harvey Bradshaw index) but who still had symptoms were considered partial responders. Patients who had no benefit after a median of 2 infusions discontinued treatment and were considered primary nonresponders. Biological activity also was assessed in all the patients using C-reactive protein (CRP) levels at baseline, at week

4 in the case of a single infusion, and at week 10 in the case of induction treatment. A decrease in CRP levels of 50% between baseline and assessment time and/or normalization of CRP levels (<3 mg/L) was classified as a biological response.

Treatment response was evaluated in all patients at 3 different time points: short term (ie, at weeks 10–14 or 4–8 weeks after the first 3 induction doses), 1 year after restart, and at the end of the follow-up evaluation.

For this analysis we defined safety as the absence of IRs. IRs can be either acute or delayed.[8] Acute reactions were graded as mild or severe. Mild acute reactions typically will subside spontaneously upon discontinuation of the IFX infusion and will not reoccur when restarted after IV steroids and/or after restarting at a slower rate. Severe reactions are defined as reactions necessitating discontinuation of the infusion owing to significant dyspnea or hypotension.

Serum Samples

Serum samples were available through systematic biobanking, which started in 1997 as part of the Vlaamse Erfelijkheidsstudie Crohn en Colitis (VLECC) (Flemish Study for Genetics Research on IBD) research program (B322201213950/S53684) All patients in our center undergo routine 10-mL serum sample collection at the infusion unit before each new infusion. These samples are divided into 500-μL aliquots and stored at -20°C. To compare the first and second IFX courses and to understand the kinetics of TL and ATI after restart, we examined serum samples at the following time points in an attempt to look for predictive factors: T-1, the last available sample during the previous course of IFX treatment (by definition at least 6 months before restart); T0, date of restart (ie, before the first re-infusion of IFX); T+1, an early sample after re-exposure to IFX: for patients with an induction regimen sample just before the second or third reinfusion of IFX, and for patients without an induction regimen at restart sample just before the second infusion at restart (with a maximum of 10 weeks [70 days] after the first reinfusion); and T+2, a later sample just before the third IFX re-start infusion for patients without an induction regimen or before the fourth infusion when restarted with the week 0, week 2, or week 6 induction.

Laboratory Methods

In addition to routine blood tests (including CRP level) all serum samples were analyzed for IFX TL and ATI using a novel homogeneous mobility shift assay (Prometheus Laboratories, Inc, San Diego, CA).[9] This method was validated in comparison with the enzyme-linked immunosorbent assay and bridging enzyme-linked immunosorbent assay methods.[10,11]

Serum IFX TLs are expressed as micrograms per milliliter. The lowest level of quantification for IFX TL is 0.91 μg/mL. Hence, all values less than 0.91 μg/mL are considered undetectable. For statistical analysis, 0.30 μg/mL is used for all TL values less than 0.91 μg/mL or for undetectable values.

ATI are expressed as units per milliliter. At the time these data were collected, for the lowest level of quantification a conservative cut-off value of 7.95 U/mL was applied. The current lower level of quantification of the assay is 3.1 U/mL. Hence, all values less than 7.95 U/mL were considered undetectable for ATI. For statistical analysis, a value of 3 U/mL was used for undetectable values.

Statistical Analysis

All data were entered in a central database using Excel (Microsoft, Redmond, WA) and analyzed statistically using SPSS version 17.0 (SPSS, Chicago, IL). The statistical analysis compiled descriptive statistics including percentages for discrete variables, and means, medians, and ranges for continuous variables. Kaplan–Meier survival analysis was used to describe time-to-event analyses. Cox regression analysis was used to test for significance of TLs as a continuous variable. To determine the optimal cut-off value of early TLs for response a receiver operating curve (ROC) analysis was performed. The presence of ATIs was used as a dichotomous variable: present or absent. For this analysis, the Mann–Whitney *U* test was used.

Univariate analyses and logistic regression analysis were performed to look for factors predicting response and IR. The results from the univariate analysis were expressed as a hazard ratio (HR) with 95% confidence intervals (CIs) and the corresponding *P* value. Stepwise logistic regression was performed using generalized linear models to test for a dichotomous outcome (response or no response) of the different clinical and biologic variables. Statistical significance was inferred at a *P* value of .05.

Results

Baseline demographics and detailed characteristics of both the first and second IFX courses are summarized in Table 1. Unlike in the second IFX course in which every patient received maintenance treatment, during the first treatment episode patients were treated with IFX in different modalities: episodic IFX infusions in 55%, maintenance IFX after an initial course of episodic IFX in 12%, and with maintenance IFX from the start in 33% according to standards and local reimbursement criteria at the time when the first IFX infusion was administered.

Most patients (n = 100; 78%) were restarted on IFX after the first course was discontinued for remission, pregnancy, or the patient's decision (temporary loss of follow-up evaluation). However, and notably, 28 patients (22%) were restarted on IFX after prior clinical and biologic LOR despite dose optimization (n = 23) and after IFX had been discontinued because of a

Table 1. Baseline Patient Demographics and Characteristics of the First and Second IFX Course

	Total (N = 128)	Crohn's disease (n = 105)	Ulcerative colitis (n = 23)
Male, n (%)	57 (44.5)	44 (42)	13 (56.5)
Age at first IFX infusion, *y* (range)	33.5 (14.4–70.2)	29.5 (14.4–65.2)	34 (14.8–71)
Interval from diagnosis to start of IFX, *mo* (range)	45.5 (7.8–142)	47.6 (7.8–142)	40 (9.4–79.1)
Treatment modality of first IFX course			
Episodic only	70 (54.6%)	58 (55.2%)	12 (52.1.%)
+Number infusions, median (range)	3 (1–15)	3 (1–15)	2 (1–6)
First episodic then maintenance	16 (12.5%)	15 (14.3%)	1 (4.3%)
Maintenance from the start	42 (32.8%)	32 (30.5%)	10 (43.5%)
Duration of first IFX treatment, *mo*	11 (0–92)	12.3 (0–92)	8.6 (0–35)
Characteristics of start of first IFX course			
IV steroid prophylaxis	19 (14.8%)	12 (11.4%)	7 (30.4%)
Induction regimen (weeks 0, 2, 6)	48 (37.5%)	42 (40%)	6 (26.1%)
IMM co-treatment	91 (71.1%)	75 (71.4%)	16 (69.5%)
Reason for discontinuation			
Remission/pregnancy	100 (78%)	80 (76.2%)	20 (87%)
LOR	23 (18%)	20 (19%)	3 (13%)
IR	5 (4%)	5 (4.7%)	0 (0%)
Duration of interval, *mo* (range)	15 (6–125)	15 (6–125)	13 (6–77)
Treatment modality of second IFX course			
Maintenance from the start	128 (100%)	105 (100%)	23 (100%)
Characteristics of start of second IFX course			
IV steroid prophylaxis	95 (74.2%)	75 (71.4%)	20 (87%)
Induction regimen (weeks 0, 2, 6)	58 (45.3%)	44 (42%)	14 (60.8%)
IMM co-treatment	84 (65.1%)	72 (68.5%)	12 (52%)

documented serious IR (n = 5). During the IFX-free interval these 28 patients were treated with a variety of other agents including investigational drugs and surgery.

Response Rate of Restarting Infliximab and Clinical Predicting Factors

Overall, restarting IFX was successful in 84.5% (at week 14), 70% (at year 1), and in 61% (at the end of the follow-up period) of patients. Clinical predictors of response were as follows: the reason for discontinuation of the first IFX course (remission vs LOR and IRs, $P < .001$) and IMM co-treatment at restart ($P = .003$) (Figure 1). The response rate of restarting IFX was not influenced by the duration of the drug holiday or by any of the other clinical (co)factors shown in Table 2, including prior episodic therapy vs maintenance from the beginning, premedication, or whether a week 0, 2, or 6 induction regimen was used.

Infusion Reactions and Clinical Risk Factors

IRs occurred in 25 patients (19.5%). Acute IRs were observed in 15 patients (11.7%). In 8 patients the

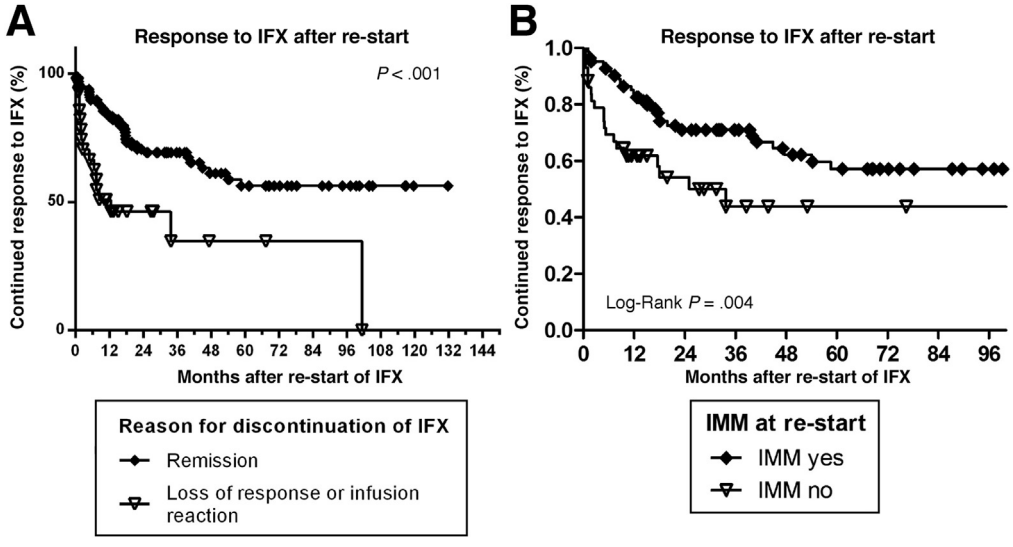

Figure 1. Kaplan–Meier curve analysis for success at retreatment over time (*A*) by reason for discontinuation and (*B*) by use of IMM or not at restart.

Table 2. Success of Restarting According to Pretreatment and Re-treatment Characteristics

Overall response	Short term 84% (108/128)	Year 1 71% (89/126)[a]	End of follow-up period 61% (78/128)
Crohn's disease	87.7% (92/105)	72.6% (76/105)	63.8% (67/105)
Ulcerative colitis	69.5% (16/23)	56.5% (13/23)	47.8% (11/23)
Treatment modality of first course			
Episodic only	81% (57/70)	66% (46/70)	51.4% (36/70)
First episodic then maintenance	81.2% (13/16)	68.7% (11/16)	68.7% (11/16)
Maintenance from the start	90% (38/42)	76% (32/42)	74% (31/42)
Characteristics of start of first IFX course			
IV steroid prophylaxis	84.2% (16/19)	73.7% (14/19)	68.4% (13/19)
Induction regimen (weeks 0, 2, 6)	93.7% (45/48)	81.2% (39/48)	70.8% (34/48)
IMM co-treatment	86.8% (79/91)	74.7% (68/91)	65.9% (60/91)
Reason for discontinuation of first IFX course			
Remission	**91%[b] (91/100)**	**77.5%[b] (76/98)**	**66%[b] (66/100)**
LOR or IR	**62% (17/28)**	**45% (13/28)**	**41.3% (12/28)**
Characteristics of start of second IFX course			
IV steroid prophylaxis	81% (77/95)	72% (67/93)	63.1% (60/95)
Induction regimen (weeks 0, 2, 6)	80.7% (46/57)	63.6% (35/55)[a]	61.4% (35/57)
IMM co-treatment	**91.6%[c] (77/84)**	**74.7%[c] (62/83)**	**66.6%[c] (56/84)**
No IMM co treatment	70.4% (31/44)	63.6% (28/44)	50% (22/44)

NOTE. Bold denotes statistical significance.
[a]For 1 patient year 1 was not reached, for 1 patient no year 1 data were available.
[b]Response rates are different for patients stopped for remission vs patients stopped owing to LOR or IR ($P < .001$).
[c]Response rates are different for patients on IMM co-treatment at restart vs patients not on concomitant IMM treatment ($P < .05$).

reaction was graded mild, and in 7 patients as severe, leading to discontinuation of the IFX treatment. Thirteen of the 15 reactions occurred despite prophylaxis. Ten of the 15 acute reactions were observed during the second or third IFX (re)infusion, but 2 reactions occurred later, more specifically after the 9th and 10th infusion, notably 8 and 10 months after the discontinuation of azathioprine. Ten patients (7.8%) experienced delayed IRs. Delayed reactions occurred a median of 9 days after the IFX infusion (range, 5–12 d). The onset of these reactions was after a median of 3 infusions (range, after infusions 1–8). Interestingly, the 4 patients not on concomitant azathioprine experienced a delayed reaction after the first (3 patients) or second (1 patient) IFX infusion. Two patients developed a delayed reaction later after restarting the sixth and eighth infusions. These reactions occurred 4 and 9 months after discontinuation of azathioprine and methotrexate. Interestingly, IMM co-treatment was the only clinical predictor of preventing an IR ($P < .01$). None of the other factors including IV steroid premedication had a protective effect in terms of preventing IRs (Supplementary Table 1).

Role of Trough Levels and Antibodies

Median TL and ATI at T+1 (and T+2) were significantly different in responders compared with non-responders (Supplementary Figure 1 and Supplementary Table 2). Cox regression analysis showed that both short-term and long-term responses correlated significantly with higher TLs at T+1 and T+2 as well as the absence of ATI, as a dichotomous variable, at T+1 and T+2. Figure 2 shows the dose-response curve for TLs at T+1 (divided in TL quartiles) at different time points. ROC curve analysis of TLs at T+1 yielded a cut-off value of greater than 2 μg/mL as an optimal value to predict long-term response (Supplementary Figure 2). At the end of the first IFX course (T-1), ATIs were detected in 13.3% of patients. At the time treatment was restarted (T0), all patients had undetectable ATIs (n = 124). After re-exposure to IFX, ATIs were detected in 40% (31 of 77) at T+1 and 29% (19 of 65) at T+2 (Figure 3). ATI values at T+1 and T+2 correlated negatively with short-term and long-term responses and detectable ATIs correlated with IRs. Because 60% to 70% of patients have undetectable values for ATIs, ATIs at T+1 and T+2 did not correlate as a continuous variable. ROC curve analysis for ATI at T+1 showed that the optimal cut-off value for predicting response was the absence of detectable ATIs (Supplementary Table 2).

Clinical and Biologic Factors Combined

Stepwise conditional regression analysis included the following factors: reason for discontinuation (LOR or other), IMM at restart, re-induction, TL and ATI at T+1 detectable or not (used as a dichotomous variable) was performed for the different co-primary end points. For short-term response, ATI at T+1 was a negative predictive factor (HR, 0.14; 95% CI, 0.026–0.74; $P = .021$) and co-treatment with IMM at restart was a positive predictive factor (HR, 6; 95% CI, 1.3–27; $P = .019$). Positive predictors for long-term outcome were the reason for discontinuation (pregnancy and/or remission vs LOR and/or IR) (HR, 2.70; 95% CI, 1.09–6.67; $P = .033$), and adequate TL at T+1 (HR, 2.94; 95% CI,

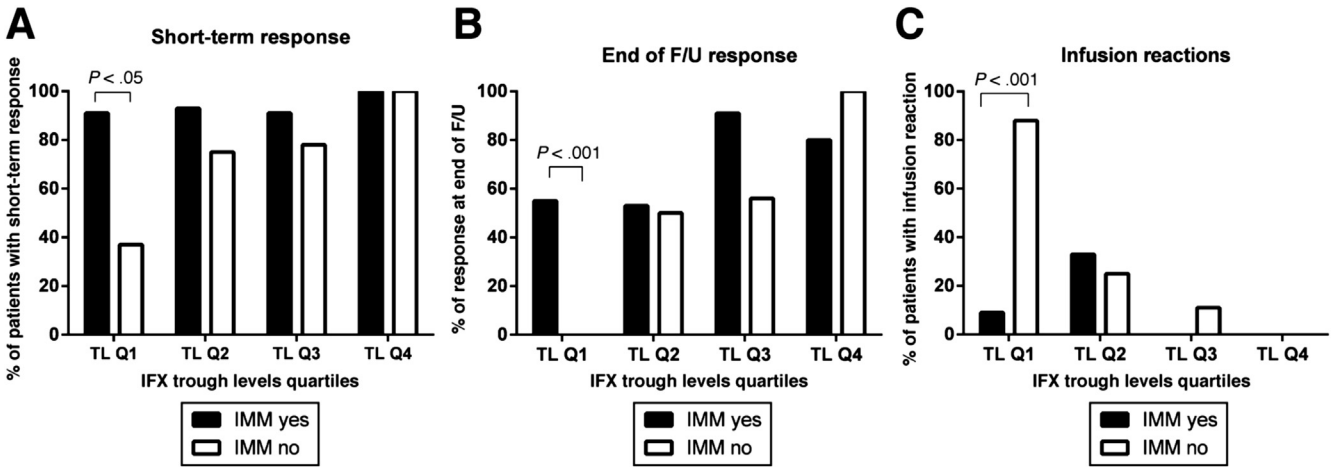

Figure 2. Response rates (*A*) short term and (*B*) at the end of follow-up evaluation, and (*C*) risk of IR according TL at T+1 in quartiles with and without IMM co-treatment. TLs at T+1 were divided into quartiles (TL Q1, 0.20–0.36 μg/mL; TL Q2, 0.36–5.23 μg/mL; TL Q3, 5.23–17.34 μg/mL; and TL Q4, 17.34–41.2 μg/mL). Response rate and risk of IR are given for each TL quartile both for patients on concomitant IMM or not on concomitant IMM treatment (no IMM). Statistically significant differences were seen for IMM vs no IMM only in the lowest quartile.

1.18–7.69; $P = .021$) (Table 3). The overall median TL at T+1 did not differ in patients with IMM co-treatment (4.9 μg/mL [interquartile range, 0.4–17.9] or without (5.4 μg/mL [interquartile range, 0.2–11.3]; $P = .479$). However, in the subgroup of patients with the lowest quartile of the TL (T+1), the combination treatment with IMM at restart resulted in significantly higher TLs (Figure 2). The only significant predictor of a safe restart was the absence of ATI after restart. Patients with detectable ATIs at T+1 were more likely to experience an IR (HR, 7.7; 95% CI, 1.88–31.3; $P = .004$). The median ATIs at T+1 were lower in patients with IMM at restart (median: undetectable [or arbitrarily set at 3 U/mL]) (interquartile range, 3–7.9 U/mL) compared with 5.6 U/mL (interquartile range, 3–38.9 U/mL) in patients without IMM at restart ($P = .027$). These findings underscore the importance of (re)starting IFX with IMM (if possible).

Discussion

We studied the short- and long-term outcome of a large consecutive IBD cohort that was retreated with IFX after a drug holiday. Our results show that restarting IFX in this high-risk group is effective both short term and long term and is relatively safe. Clinically important factors that determined the success of restarting IFX included the reason for discontinuation of the first course and the use of concomitant IMM therapy at restart. Nevertheless, even in refractory patients in whom IFX initially was stopped for LOR despite dose optimization or for IR good short-term responses and moderate long-term response rates were seen. Furthermore, we showed that pharmacologic monitoring (ie, IFX TLs and ATIs) early after restarting IFX can guide physicians to predict the long-term efficacy and safety of restarting IFX, respectively. Concomitant IMM therapy attenuates ATI formation and therefore prevents IR and LOR.

This study showed several new findings. Restarting IFX after a history of prior episodic therapy can be safe and effective. Most striking is probably the fact that response to IFX can be regained in a subset of patients who previously had lost response to IFX and failed several other treatments thereafter. In addition, this study showed that measuring TLs and ATIs helps to predict the long-term efficacy and safety of restarting

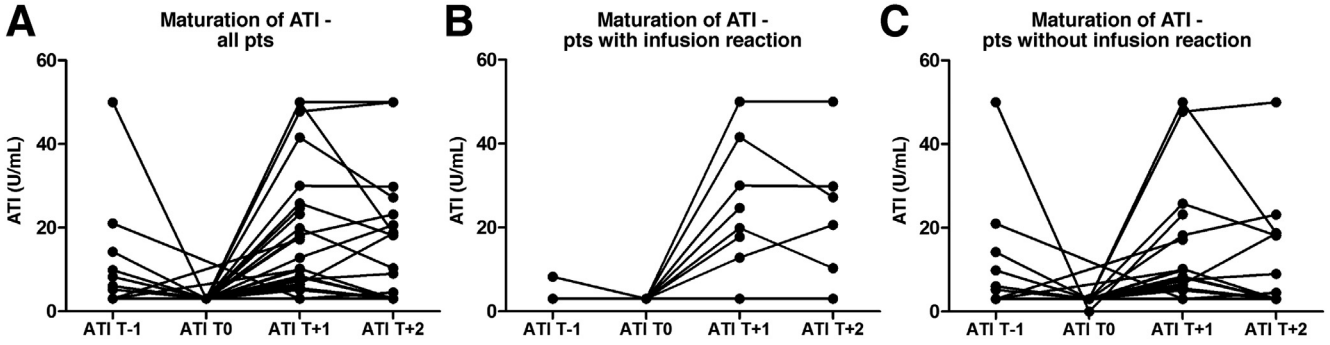

Figure 3. Maturation of ATI at the different time points T-1, T0 (disappearing), T+1, and T+2 (reappearing). (*A*) ATI values of all patients. (*B*) ATI values of patients with IRs. (*C*) ATI values for patients without IR. On the y axes, all values above 50 IU/mL were set to 50 IU/mL maximum. Only patients are shown with serum available at T+1. pts, patients.

Table 3. Clinical and Biologic Factors Predicting Short- and Long-Term Response of IFX Restarting

Response (%)	Short term	Year 1	End of follow-up period	HR (95% CI); *P* value[a]
ATI T+1 detectable (n = 31)	71%[a]	54.8%	38.7%	0.14 (0.026–0.74); .021
IMM at restart (n = 84)	91.6%[a]	74.7%	66.6%	6.00 (1.3–27); .019
Reason for discontinuation (remission) (n=100)	90%	77.5%	66.6%[a]	2.70 (1.09–6.67); .033
TL T+1 > 2 μg/mL (n = 43)	93%	74%	70%[a]	2.94 (1.18–7.69); .021

[a]The values in the last column correspond to the first 2 lines of short-term response and the last 2 lines of end of follow-up period.

IFX. An IFX TL greater than 2 μg/mL and an undetectable ATI early after restart are predictive of response. The combination of clinical factors and these pharmacologic factors predict long-term response and an absence of IRs. Concomitant IMM therapy is important for the long-term response but only in those patients with low TL early after restart.

IRs were observed in 19.5% of patients. The majority of these IRs occurred during or after the first 3 reinfusions. Concomitant IMM therapy (azathioprine/6-mercaptopurine or methotrexate) therefore always should be used, if feasible, when considering IFX retreatment. Another striking finding in this study was that we could not find any protective effect from IV premedication with hydrocortisone and oral antihistamines despite the fact that this practice is used widely. This is in contrast to the study by Farrell et al,[12] however, this study was better designed to answer this particular question because it was (partially) randomized for steroid administration or not.

In clinical practice, TL and ATI are not always readily available. However, measuring a TL early after restarting IFX is very valuable as we show in this study and allows early optimization in case of low levels of IFX TL. A recent study comparing different assays that measure TL and ATI stressed the importance of the validation of these tests among the different laboratories.[11,13] In addition, given the wider range of (low) values, TL testing, as opposed to ATI, is more reliable as a continuous variable. Figure 2 clearly illustrates the relation between early TL, split up in different quartiles, and short-term and long-term response rates. This is in line with other emerging evidence showing that early TL testing predicts mucosal healing and long-term response in IFX, adalimumab, and certolizumab pegol.[14–18] Figure 2 also illustrates and clarifies the interplay between IMM co-treatment and TL. Different studies have shown higher IFX and adalimumab TLs in patients on combination treatment with either azathioprine/6-mercaptopurine or methotrexate. However, there are many conflicting data regarding the clinical superiority of combination therapy vs monotherapy, especially in patients who failed IMM in the past.[19] We showed, in a population that failed IMM therapy, that combination therapy is superior only in patients with TLs in the lowest quartile early after restarting with regard to long-term efficacy and safety. This is in line with previously reported data.[20] Therefore, we recommend TL testing and, when adequate TLs are found, anti-TNF could be continued as monotherapy.

The serial measurements in these patients also confirm the dynamic nature of ATI formation and detection. ATIs detected during the first course of IFX treatment were no longer detectable after the drug holiday.[21] However, ATIs can re-appear quickly and in high titers when the patient is re-exposed to IFX. The production of ATI by memory B cells can be suppressed by concomitant IMM therapy as illustrated recently.[22] The kinetics of antidrug antibody formation recently was reported by another group as well.[21,22] We confirmed that the presence of ATI is important for long-term efficacy, including for patients who restarted after a long drug holiday.

Our study had limitations. Although the serum blood samples were collected prospectively, the clinical data were collected retrospectively. In addition, patients were treated in a nonrandomized fashion, including episodic therapy during the first IFX treatment course. However, this reflects a real-life situation and enabled studying different potential risk factors. We believe that the large consecutive cohort, the long-term follow-up evaluation (compared with randomized controlled trials), and the careful multivariate analysis of all risk factors allows for identification of predictive factors.

To conclude, we show that restarting maintenance IFX is highly efficacious both short and long term, including in patients with prior episodic therapy. However, concomitant IMM treatment at the beginning seems key. We provide evidence that early testing of TLs and ATIs allows for predicting a reliable long-term prognosis on both efficacy and safety. Discontinuation of concomitant IMM therapy might be considered in patients with high early TLs. Our data do not support systematic premedication with IV steroids upon restarting. This study contributes to the emerging evidence of using therapeutic drug monitoring of IFX therapy in clinical practice. Prospective trials are underway and should confirm the validity of pharmacokinetic-based treatment paradigms of biologics (eg, Study Investigating Tailored Treatment With Infliximab for Active Crohn's Disease [TAILORIX]).[23,24]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2014.01.033.

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Reprint requests
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Conflicts of interest
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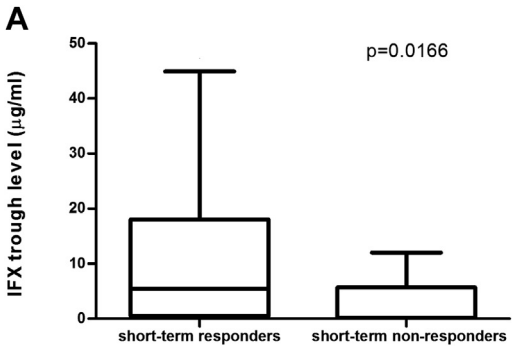
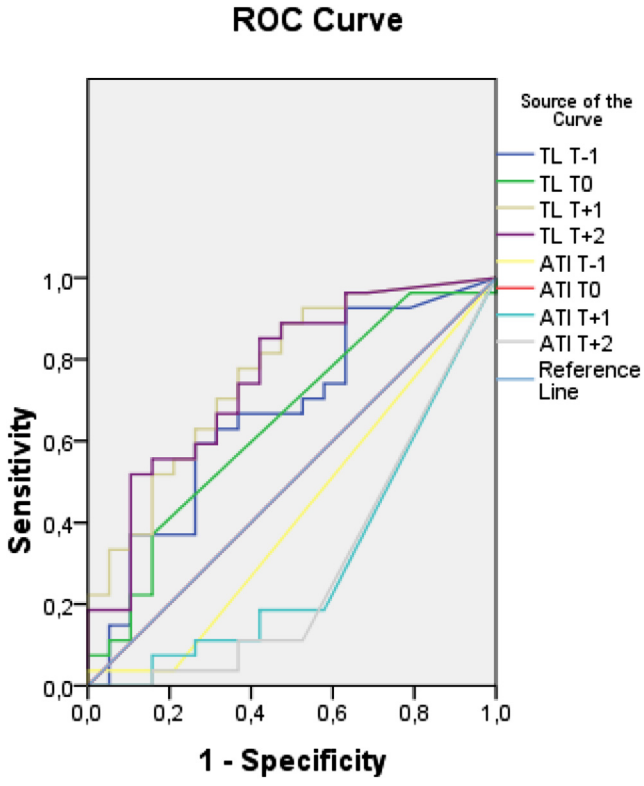


Supplementary Figure 1. Box plots of TL (median µg/mL + 95% CI) measured early after restart (T+1) comparing responders and non-responders (*A*) short term and (*B*) at the end of the follow-up period.



Supplementary Figure 2. ROC curve for TL and ATI at all time points and long-term response according to Kaplan–Meier analysis. The AUC for TL T+1 was 0.764 (95% CI 0.624–0.904); asymptotic significance was set at $P = .003$.

Supplementary Table 1. Safety of Restarting IFX: According to Pretreatment and Re-treatment Characteristics

IR type and % risk (N)	Total, 19.5% (N = 25)	Serious, 12.5% (N = 16)	Acute, 11.7% (N = 15)	Delayed, 7.8% (N = 10)
Treatment modality of first course				
Episodic only (N = 70)	28.5% (20)	18.5% (13)	17% (12)	11.4% (8)
Maintenance after episodic (N = 16)	12.5% (2)	6.2% (1)	0% (0)	12.5% (2)
Maintenance from the start (N = 42)	7% (3)	4.7% (2)	4.7% (2)	2.4% (1)
Characteristics of start of first IFX course				
IV steroid prophylaxis (N = 16)	18.7% (3)	6.25% (1)	18.7% (3)	0% (0)
Induction regimen (weeks 0, 2, 6) (N = 48)	10.4% (5)	4.2% (2)	8.3% (4)	10% (1)
IMM co-treatment (N = 98)	18.3% (18)	10.2% (10)	11.2% (11)	70% (7)
Reason for discontinuation				
Remission (N = 100)	15% (15)	7% (7)	10% (10)	5% (5)
LOR (N = 23)	28% (7)	30.4 (7)	17.4% (4)	13% (3)
IR (N = 5)	12% (3)	40% (2)	20% (1)	40% (2)
Characteristics of start of second IFX course				
IV steroid prophylaxis (N = 95)	21% (20)	15.7 (15)	12.6% (12)	8.4% (8)
Induction regimen (weeks 0, 2, 6) (N = 57)	24.5% (14)	19.% (11)	15.8% (9)	8.7% (5)
IMM co-treatment (N = 84)	12%[a] (10)	4.7%[a] (4)	6% (5)	5.9% (5)
No IMM co-treatment (N = 44)	34%[a] (15)	27%[a] (12)	22.7% (10)	11.3% (5)

[a]*P* value was less than .01 for comparison of incidence of total IR on IMM co-treatment vs no IMM at restart.

Supplementary Table 2. ATI T+1 (% Undetectable; Median + Interquartile Range) for Responders and Nonresponders (Short Term and End of Follow-up Evaluation)

	Short-term response		Response at end of follow-up period	
	Yes	No	Yes	No
Undetectable	67% (81/121)	18% (2/11)	74.5% (35/47)	36.6%
Detectable	33% (40/121)	82% (9/11)	25.5% (12/47)	63.3%
Median (IQR), *μg/mL*	3 (3–7.8)	19.8 (6.7–196.1)	3 (3–7.3)	7.9 (3–28.6)

NOTE. For statistical analysis, undetectable ATI were set to 3 (lower limit of detection).
IQR, interquartile range.