Outcomes 7 Years After Infliximab Withdrawal for Patients With Crohn's Disease in Sustained Remission

Catherine Reenaers,[*] Jean-Yves Mary,[‡] Maria Nachury,[§] Yoram Bouhnik,[‖] David Laharie,[¶] Matthieu Allez,[#] Mathurin Fumery,[**] Aurélien Amiot,[‡‡] Guillaume Savoye,[§§] Romain Altwegg,[‖‖] Martine Devos,[¶¶] Georgia Malamut,[##] Arnaud Bourreille,[***] Bernard Flourie,[‡‡‡] Philippe Marteau,[§§§] Lucine Vuitton,[‖‖‖] Benoît Coffin,[¶¶¶] Stéphanie Viennot,[###] Jérôme Lambert,[‡] Jean-Frédéric Colombel,[****] and Edouard Louis,[*] and the Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif

*Gastroenterology Department, Centre Hospitalier Universitaire de Liège, Liège, Belgium; [‡]INSERM U717, Biostatistics and Clinical Epidemiology, [‖]Hôpital Beaujon, [#]Hôpital Saint-Louis, [¶¶¶]Hopital Louis Mourier, Université Paris Diderot-Paris 7, Paris, France; [§]Centre Hospitalier Régional Universitaire de Lille, Université Lille Nord de France, Lille, France; [¶]Hôpital Haut-Lévêque, INSERM U853, Université Bordeaux 2, Bordeaux, France; [**]Centre Hospitalier Universitaire d'Amiens, Hôpital Nord, Amiens, France; [‡‡]Hôpital Henri Mondor, Paris Est-Créteil Val de Marne University, Creteil, France; [§§]Hôpital Charles Nicolle, Université de Rouen, Rouen, France; [‖‖]Hôpital Saint-Eloi, University Hospital of Montpellier, Montpellier, France; [¶¶]Faculty of Medicine and Health Science, University of Ghent, Ghent, Belgium; [##]Hôpital Européen Georges Pompidou Assistance Publique-Hôpitaux Paris, Université Paris Descartes-Sorbonne Paris Centre, Paris, France; [***]Centre Hospitalier Universitaire de Nantes, Hôtel-Dieu, Nantes, France; [‡‡‡]Centre Hospitalo-Universitaire Lyon-Sud, Hospices Civils de Lyon, Pierre Bénite, France; [§§§]Hôpital Lariboisière, Assistance Publique-Hôpitaux Paris, University Denis Diderot, Paris, France; [‖‖‖]Hôpital Universitaire de Besançon, Besançon, France; [###]Hôpital Universitaire de Caen, Caen, France; [****]Icahn School of Medicine at Mount Sinai, Feinstein Inflammatory Bowel Disease Clinical Center, New York, New York

BACKGROUND & AIMS: **Little is known about long-term outcomes of patients with Crohn's disease (CD) after infliximab withdrawal. We aimed to describe the long-term outcomes of patients with CD in clinical remission after infliximab treatment was withdrawn.**

METHODS: **We performed a retrospective analysis of data from the 115 patients included in the infliximab discontinuation in patients with CD in stable remission on combined therapy with antimetabolites (STORI) study, performed at 20 centers in France and Belgium from March 2006 through December 2009. The STORI cohort was a prospective analysis of risk and factors associated with relapse following withdrawal of maintenance therapy with infliximab, maintained on antimetabolites, while in clinical remission. We collected data from the end of the study until the last available follow-up examination on patient surgeries, new complex perianal lesions (indicating major complications), and need for and outcomes of restarting therapy with infliximab or another biologic agent. The de-escalation strategy was considered to have failed when a major complication or infliximab restart failure occurred.**

RESULTS: **Of the 115 patients initially included, data from 102 patients (from 19 of the 20 study centers) were included in the final analysis. The median follow-up time was 7 years. Twenty-one percent of the patients did not restart treatment with infliximab or another biologic agent and did not have a major complication 7 years after infliximab withdrawal (95% CI, 13.1–30.3). Among patients who restarted infliximab, treatment failed for 30.1% 6 years after restarting (95% CI, 18.5–42.5). Overall, at 7 years after stopping infliximab therapy, major complications occurred in 18.5% of patients (95% CI, 10.2–26.8) whereas 70.2% of patients had no failure of the de-escalation strategy (95% CI, 60.2–80.1). Factors independently associated with major complications were upper-gastrointestinal location of disease, white blood cell count ≥ 5.0 × 10^9/L, and hemoglobin level ≤12.5 g/dL at the time of infliximab withdrawal. Patients with at least 2 of these factors had a more than 40% risk of major complication in the 7 years following infliximab withdrawal.**

Abbreviations used in this paper: CD, Crohn's disease; CDAI, CD activity index; CRP, C-reactive protein; IFX, infliximab; IQR, interquartile range; 6TGN, 6-thioguanine nucleotides; STORI, infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors; TNF, tumor necrosis factor.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2017.09.061

CONCLUSIONS: **In a long-term follow-up of the STORI cohort (7 years) one fifth of the patients did not restart infliximab or another biologic agent and did not develop major complications. Seventy percent of patients had no failure of the de-escalation strategy (no major complication and no failure of infliximab restart).**

Keywords: Anti-TNF; IFX; GETAID; Success.

Therapeutic strategies in Crohn's disease (CD) have evolved considerably in the past few decades. The recognition that subclinical and undertreated inflammation can lead to poor outcomes has underpinned a shift in treatment goals from symptomatic control to sustained clinical and endoscopic remission.[1–4] As a result of this change in the treatment paradigm, there has been an exponential increase in the number of patients exposed to higher levels of immunosuppression earlier in their disease course, usually in the form of anti–tumor necrosis factor (TNF) monotherapy or combination therapy.[5,6] However, there are costs[7] and safety[8] issues associated with these strategies, and, therefore, determining if, when, and in whom immunosuppressive therapies should be discontinued is actively debated. Many studies have reported on relapse rates after drug de-escalation, especially with anti-TNFs, in the hope of identifying a subgroup of patients in whom treatment could be reduced to the minimal effective therapy needed to maintain remission. The infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors (STORI) trial[9] was a prospective study in CD looking at the risk and predictors of relapse after anti-TNF maintenance therapy withdrawal. Approximately 50% of patients who were treated for at least 1 year with infliximab (IFX) and an antimetabolite agent experienced a relapse within 1 year after discontinuation of IFX. Patients at low risk of relapse could be identified using a combination of clinical and biologic markers. Re-induction with infliximab was effective and well tolerated in the majority of patients: just before the third infliximab infusion, 38 of 43 patients (88%) were in remission and 42 of 43 (98%) had a clinical response. Several withdrawal studies have been published since then and a recent systematic review concluded that approximately 50% of patients who discontinued anti-TNF agents after combination therapy maintained remission at 24 months; however, longer-term data still are missing.[10] The aim of the present study was to describe the long-term results of the STORI trial and to identify predictors of poor outcomes.

Patients and Methods

Patient Recruitment

All the patients included in the STORI trial[9] were eligible for inclusion in this long-term follow-up study. In summary, the STORI cohort was a prospective multicenter cohort conducted in 20 centers in France and Belgium between March 2006 and December 2009. A total of 115 patients on combination therapy with IFX and an antimetabolite (azathioprine, mercaptopurine, or methotrexate) for at least 1 year and in steroid-free clinical remission for at least 6 months were included. IFX was discontinued and patients were followed up prospectively. Baseline clinical and demographic characteristics were collected prospectively at the time of IFX withdrawal. Clinical index, endoscopic index, and biologic data also were collected prospectively at the time of withdrawal including CD activity index (CDAI), CD Endoscopic Index of Severity, hemoglobin, hematocrit, white blood cell count, platelet count, erythrocyte 6-thioguanine nucleotides (6TGN) (in patients treated with purine analogues), high-sensitivity C-reactive protein (CRP), IFX trough levels, anti-infliximab antibodies, and fecal calprotectin levels. During the STORI study follow-up period, relapse was defined as a CDAI increase greater than 250 or greater than 150 over 2 consecutive visits with a differential of at least 70 points from baseline. IFX subsequently was resumed. The short-term outcome after IFX resumption was recorded. In addition to clinical events observed during the STORI study, those occurring after the end of STORI (December 2009) were recorded retrospectively by reviewing the clinical notes of the patients through the last available follow-up evaluation. They included a surgical resection, the occurrence or recurrence of a complex perianal lesion,[11] or the need to restart biologics for a CD flare (IFX, adalimumab, or other biologics). In the subgroup of patients who restarted IFX, assessments included acute or delayed infusion reactions, the need for IFX optimization, treatment-related side effects, and a second interruption of IFX therapy owing to either nonresponse, loss of response, or remission.

Outcomes

The following 3 types of outcomes were observed: (1) need to restart IFX or any biologic, (2) IFX restart failure, and (3) major complication. Either of the second 2 outcomes was considered to be a failure of the de-escalation strategy. IFX restart failure was defined as cessation of IFX owing to an acute or delayed infusion reaction, to either nonresponse or loss of response, or secondary to IFX-related side effects. A major complication was defined as the occurrence of a surgical

resection or new complex perianal lesions, defined by the Hughes[11] classification, before or after IFX resumption.

Follow-Up Evaluation

Follow-up evaluation began at the time of IFX withdrawal in the STORI study, except when evaluating IFX restart failures, for which follow-up evaluation began at the time of IFX resumption. The following events were recorded: any biologic resumption, IFX restart failure, and any major complication. For patients who experienced an event, the time-to-event was the delay between the beginning of the follow-up period and event occurrence. For a patient who did not experience an event, follow-up evaluation was censored at the end of the study (December 31, 2014) or at the date of last contact. In addition, patients who started adalimumab after IFX withdrawal without retrying IFX had their follow-up evaluation censored at the time of first adalimumab treatment for analyses of major complications. Similarly, patients who had restarted IFX but were switched electively to adalimumab without a specific medical reason (eg, patient or doctor preference) had their follow-up evaluation censored at the time of adalimumab treatment for analyses of IFX restart failure or major complications.

Statistical Analysis

Patient characteristics were described through frequencies (proportion) or medians (interquartile range [IQR]). The cumulative incidence of starting or restarting a biologic and of secondary IFX failure among patients who had restarted IFX, estimating the marginal probability of the event,[12] was calculated, taking into account major complications as a competing event. These results were presented as percentages with 95% CIs, number of events, number of major complications, and number of patients at risk at prespecified time points after IFX withdrawal. For major complications or for strategy failure, time-to-event curves were derived through the Kaplan–Meier method and were described using the number of events/number of patients, percentages of event-free survival with 95% CIs, and the number of patients at risk at prespecified time points after IFX withdrawal.

Factors associated with time to major complication were studied through univariable and multivariable proportional hazards models. Continuous variables were categorized into 2 or 3 classes as in the STORI study. After univariable analysis, all variables with a P value less than .30 were included in the multivariable analysis. Prognostic factors were derived through backward selection using the likelihood ratio test and their relation to time-to-event was expressed as a hazard ratio with 95% CI. The proportionality assumption was checked graphically.

Results

Study Population

A total of 115 patients recruited at 20 Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif centers initially were included in the STORI cohort.[9] All the centers but one agreed to participate in this long-term follow-up cohort of 102 patients. Thirteen patients from 1 center were not included. The baseline demographic, clinical, biologic, and endoscopic characteristics of the 102 patients are described in Table 1. All patients were in clinical remission (CDAI $<$ 150) and most had low CD Endoscopic Index of Severity scores

Table 1. Patients Characteristics (N = 102)

Demographic, clinical, biological, and endoscopic characteristics of the patients (n = 102)	N (%) or median (IQR)
Male	43 (42)
Age, *y*	32 (25–39)
Disease duration, *y*	7 (4–12)
Active smoker	39 (38)
Disease site (N = 101)	
Ileal	12 (12)
Colonic	57 (56)
Ileocolonic	38 (32)
Upper gastrointestinal tract	9 (9)
Perianal lesions	37 (36)
Intestinal stricture at infliximab initiation (N = 101)	6 (6)
Intra-abdominal fistulizing disease at infliximab initiation	1 (1)
Previous surgical resection	22 (22)
Treatment history	
Methotrexate	17 (17)
Azathioprine/mercaptopurine	85 (83)
Years since infliximab initiation	2.2 (1.6–3.2)
Anti-infliximab antibody at baseline (N = 89)	
Positive	1
Negative	40
Inconclusive	58
Infliximab trough level	3.8 (1.8–8.2)
Endoscopic variable	
CDEIS	1.0 (0–3)
CDEIS = 0	31 (30)
Remaining ulcers	39 (38)
Biologic variables	
Hemoglobin level, *g/L*	136 (129–144)
White blood cell count, 10^9/L	6.2 (5.0–7.7)
Platelet count, 10^9/L	273 (233–312)
hsCRP level, *mg/L* (n = 96)	2.0 (0.8–4.8)
Fecal calprotectin level, $\mu g/g$ (n = 75)	51 (30–350)

CDEIS, Crohn's Disease Endoscopic Index of Severity; hsCRP, high-sensitivity CRP.

(median, 1.0; range, 0–3), hsCRP levels (median, 2.0; range, 0.8–4.8; n = 96), and fecal calprotectin levels (median, 51; range, 30–350; n = 75). The distribution of baseline characteristics as well as the relapse-free survival curve of the 13 patients not included are shown relative to the study sample in Supplementary Table 1 and Supplementary Figure 1.

Patient Follow-Up Evaluation

The median follow-up time was 83 months (IQR, 71–93 mo). At 7 years, 70.2% (95% CI, 60.2%–80.1%) had not experienced a failure of the de-escalation strategy (IFX restart failure or major complication). The detailed outcomes of the patients are described in Table 2 and a general overview is shown in Figure 1.

Need to restart a biologic. Twenty-two patients never restarted IFX or another biologic and did not experience a major complication after a median follow-up period of 78 months (IQR, 58–96 mo). Overall, 21.6% (95% CI, 13.1%–30.3%) of patients did not restart a biologic and did not have a major complication at 7 years after IFX withdrawal. Among these patients, 7 were still on azathioprine monotherapy, 6 were treated with methotrexate, and 9 received no treatment. Eight patients experienced a major complication while not being treated with biologics after a median follow-up time of 45 months (IQR, 22–64 mo).

Seventy-two patients had to restart a biologic after a median time without IFX of 13 months (IQR, 6–33 mo). Among these patients, 6 had stopped azathioprine and received no immunomodulators at the time of failure. Sixty-four patients restarted IFX and 8 were re-treated electively with adalimumab instead of IFX. The cumulative incidence of restarting a biologic is described in Figure 2.

Outcome After Infliximab Resumption and Infliximab Restart Failure

Among the 64 patients who restarted IFX, 33 patients continued IFX for a median of 70 months (IQR, 47–83 mo). Seven patients successfully stopped IFX a second time after a median IFX treatment time of 41 months and were followed up without treatment for a median time of 28 months. Two patients resumed IFX without failure, and then electively were switched to adalimumab at 6 and 14 months after IFX resumption. Among patients resuming IFX without failure, 16 required optimization of IFX treatment after a median time of 25 months (IQR, 8–55 mo). Optimization involved reduction of the infusion interval in 6 patients and an increase of the IFX dose in 10 patients.

Twenty-two patients who restarted IFX experienced a failure. Ten patients had an optimization of IFX treatment before the failure. Four patients had a major complication after a median time of 38 months, and 18 (including 1 after the end of the study) had a secondary loss of response to IFX after a median treatment time of 22 months (IQR, 10–39 mo), with 6 later experiencing a major complication after a median treatment time of 23 months. The cumulative incidence of IFX restart failure was 30.1% (95% CI, 18.5–42.5) at 6 years after IFX resumption and is described in Figure 3.

Major Complications

Eighteen of 102 patients experienced a major complication after a median time of 50 months (IQR, 41–73 mo) after IFX cessation including 14 surgeries and 4 new complex perianal lesions. Among the patients undergoing surgery, 4 received no immunomodulators or biologics at the time of the failure. The time-to-major complication curve is shown in Figure 4. Overall, 18.5% (95% CI, 10.2–26.8) of patients had a major complication within 7 years after IFX withdrawal. In multivariable analysis, the factors significantly associated with an increased risk of major complication were upper gastrointestinal tract involvement, a white blood cell count $\geq$ 5.0 10^9/L, and a hemoglobin concentration $\leq$ 12.5 g/dL at the time of IFX withdrawal (Table 3). A model based on the presence or absence of each of the 3 predictors divided the patients into 3 risk groups: a low-risk group (defined by the absence of all 3 predictors) of 13 patients with a very low risk of major complications (none observed); an intermediate-risk group (defined by the presence of at least 1 predictor) of 72 patients with a moderate rate of major complications of 16.3% (range, 6.9%–25.0%) at 7 years; and a high-risk group (defined by the presence of at least 2 predictors) of 17 patients with a rate of major complications of 43.0% (range, 16.5%–69.4%) at 7 years.

Discussion

After a median follow-up time of approximately 7 years of patients in the STORI cohort, the main findings are as follows: approximately two thirds of the patients had no strategy failure, defined as the absence of IFX restart failures and major complications; close to one fifth of patients were never re-treated with a biologic and did not have a major complication; and a little less than one fifth of patients required surgery or developed a complex perianal fistula.

In most studies reporting the outcome of patients with CD after IFX withdrawal the median follow-up period was 1 to 2 years and they reported similar relapse rates to the STORI trial (approximately 50%).[9,10,13–15] Few studies reported on the long-term outcome of patients after IFX withdrawal when in clinical remission. A Danish retrospective observational study reported a low rate of remission (12%) at 10 years after the last IFX infusion.[14] A French retrospective cohort comparing the outcome of CD patients after IFX

Table 2. Detailed Outcomes of the 102 Patients

IFX restart	IFX stop	Reasons for secondary IFX stop		First event	Consequence	Second event	Failure	
							First event	Second event
No, n = 38	/	/		None, n = 22	/	/	0	0
				Adalimumab started, n = 8	Censoring	/	0	0
				Complex perianal lesion, n = 2	Major complications	/	8 major complications	1 major complication
				Surgery, n = 6	None, n = 5 Complex perianal lesson, n = 1			
Yes, n = 64	No, n = 37	/		None, n = 33	/	/	0	0
				Complex perianal lesion, n = 2	Failure	/	4 major complications	0
				Surgery, n = 2				
	Yes, n = 27	No failure, n = 9	Wish of patient, n = 1	Elective switch to ADA, n = 2	Censoring	/	0	0
			Pregnancy, n = 6					
			Remission, n = 2	None, n = 7	/			
		Failure, n = 4	Infection, n = 2	18 IFX restart failures, no major compilations	None, n = 4	/	4 IFX restart failures	0
			Oncologic issue, n = 1					
			Cutaneous side effect, n = 1					
						Surgery, n = 3		
		Failure, n = 14	Loss of response, n = 7		Change of treatment, n = 14	None, n = 4	14 IFX restart failures	6 major complications
			No response, n = 1			None, n = 1		
						Surgery, n = 2		
			Cutaneous side effect, n = 3[a]			None, n = 1		
			Infection, n = 1			None, n = 1		
			Infusion reaction, n = 1			None, n = 1		
			Myelitis, n = 1			Surgery, n = 1		

ADA, adalimumab.

[a]One occurring after the end of the study (December 31, 2014).

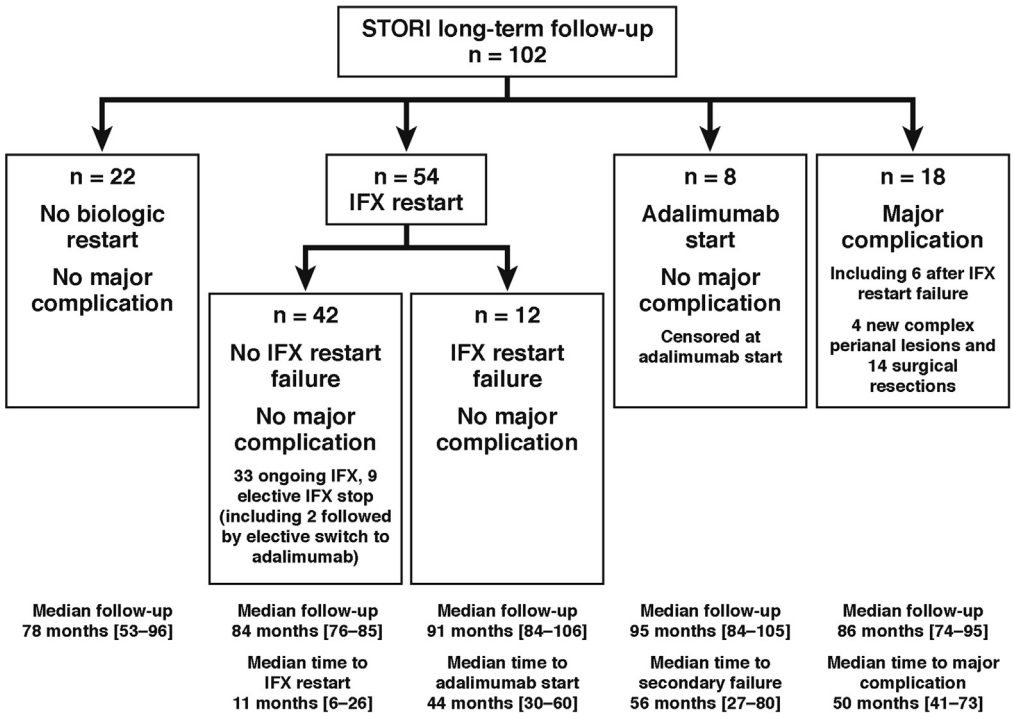
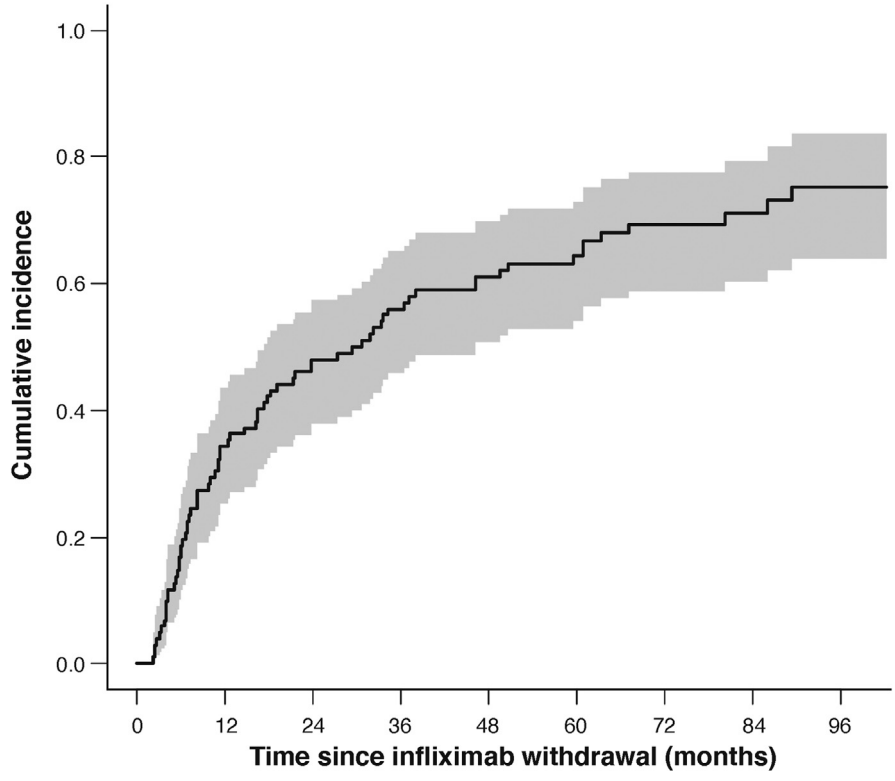


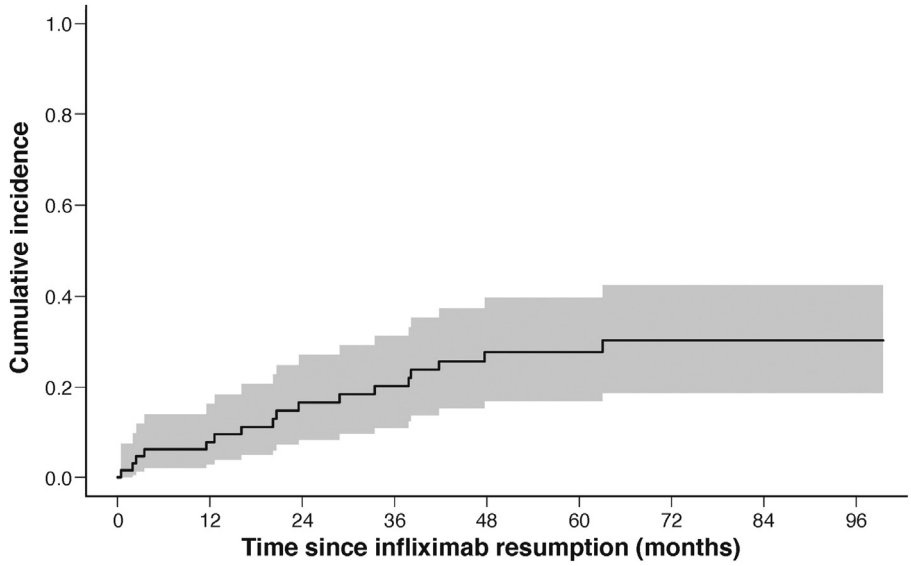
Figure 1. General view of patients' outcome.

withdrawal using induction alone or induction plus at least 1 year of maintenance therapy found that 72% of patients relapsed after a median follow-up period of 47 months in both groups.[16] A retrospective study from Leuven, Belgium, reported the lowest rates of CD relapse after IFX discontinuation while in clinical



Number at risk	102	66	51	42	32	24	18	11	3
Number events									
Anti-TNF resumption	0	35	49	57	62	65	69	70	72
Major complication	0	1	2	2	6	6	7	7	8

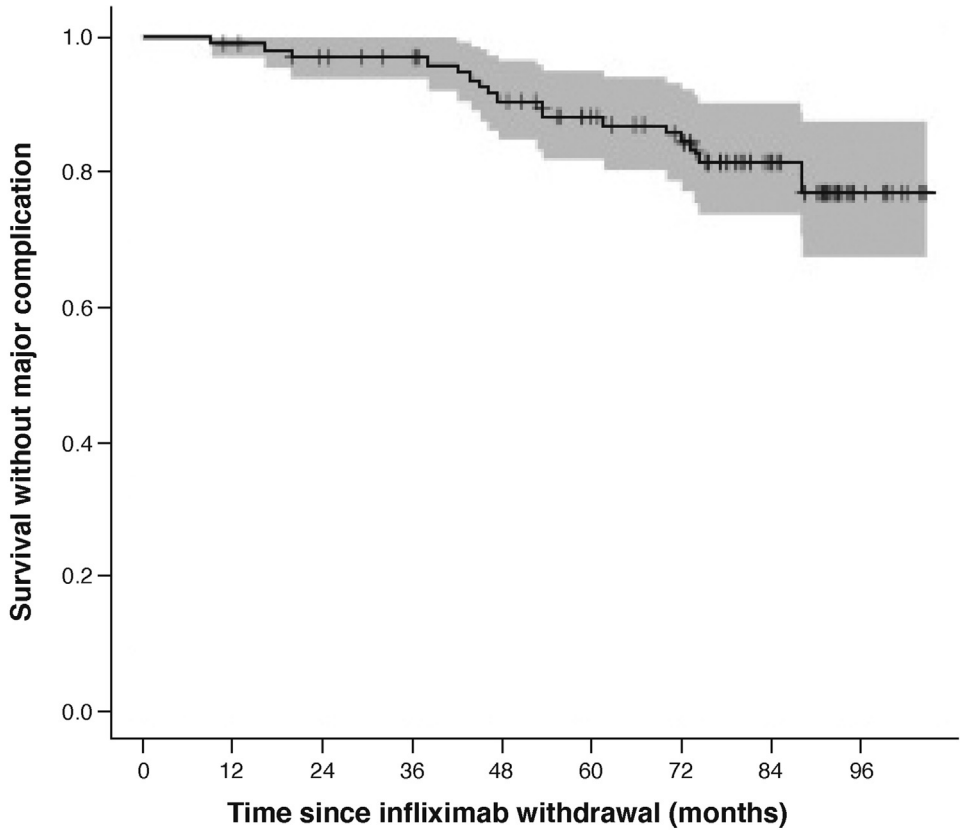
Figure 2. Cumulative incidence of biologic resumption. The cumulative incidence of biologic resumption was 34.3% (95% CI, 25.2–43.6), 56.0% (95% CI, 45.8–65.1), and 64.4% (95% CI, 54.0–73.0), respectively, at 1, 3, and 5 after IFX withdrawal.



Number at risk	64	54	45	42	34	30	16	9	1
Number failures									
IFX restart failure	0	5	10	12	16	16	17	17	17
Major complication	0	2	2	2	2	2	3	3	4

Figure 3. Cumulative incidence of IFX restart failure after resumption. Among the patients who resumed infliximab (n = 64), the cumulative incidence of IFX restart failure was 7.9% (95% CI, 2.9–16.2), 20.1% (95% CI, 11.0–31.2), and 27.7% (95% CI, 16.7–39.8), respectively, at 1, 3, and 5 years after IFX resumption.

remission with 96%, 93%, and 52% without clinical relapse after 1, 2, and 10 years, respectively.[17] The IFX regimen was heterogeneous in this cohort, with 65% receiving episodic treatment. Patients also were selected electively for treatment withdrawal in the setting of routine practice with no specific protocol. This might reflect a population with less severe disease requiring less IFX to control the disease and could explain the lower long-term relapse rate. In a preliminary Danish study, 30% higher remission rates were achieved when optimizing thiopurine treatment before stopping IFX.[18]



Number at risk	102	100	95	92	83	73	65	40	10

Figure 4. Kaplan–Meier survival without major complication curve. The patients' survival without major complication was 99.0% (95% CI, 97.3–99.8), 97.0% (95% CI, 93.6–99.6), and 88.2% (95% CI, 81.6–94.8), respectively, at 1, 3, and 5 years after IFX withdrawal.

Table 3. Independent Risk Factors of Major Complications

Risk factors	*P*	HR	95% CI
Upper GI tract involvement	.027	5.8	1.5–21.8
White blood cell count, ≥5.0 10^9/L	.002	10.5	1.3–83.0
Hemoglobin level, ≤12.5 g/dL	.014	4.1	1.5–21.8

GI, gastrointestinal; HR, hazard ratio.

In many studies, the information was restricted to clinical relapse and the need to restart IFX with no further details on the occurrence of complications or the long-term outcome after re-treatment.[14,17] In the present long-term follow-up evaluation of the STORI trial, 18% of the patients experienced a major complication (surgical resection or new complex perianal lesions) within 7 years after IFX withdrawal. Among the 18 patients with severe complications, 4 had stopped all medications and this could have promoted the need for surgery in our cohort. Schnitzler et al[19] showed similar rates of surgery in the cohort from Leuven despite IFX continuation on a scheduled basis with 10% and 20% of patients requiring surgery after a median follow-up period of 36 and 60 months, respectively. In contrast, the Hungarian cohort[15] reported higher rates of surgery during the first year after IFX cessation with 9% of patients needing surgery during that period. Not all patients were in clinical remission at the time of IFX discontinuation in this study, which could explain the high rate of short-term surgery in this population.

In our cohort, major complications occurred relatively late after IFX withdrawal, with a median time from the last IFX infusion of 45 months. This suggests the need for long-term close monitoring even in the absence of early clinical relapse to avoid later major complications after IFX cessation.

When considering biologic withdrawal, identification of predictors of failure is crucial to help identify a high-risk subgroup in whom this strategy should be avoided. In our cohort, an upper gastrointestinal location of CD, a hemoglobin level ≤ 12.5 g/dL, and a white blood cell count ≥ 5.0 10^9/L at the time of IFX withdrawal each independently were associated significantly with major complications after IFX cessation. These findings are consistent with the results from different population-based studies showing that the presence of upper gastrointestinal involvement was associated strongly with progression toward strictures or penetrating disease[20,21] and subsequent surgery.[22,23] Meta-analyses have shown an inverse correlation between leukocyte count and 6TGN level.[24] There is a clear association between clinical remission and not only higher 6TGN concentrations,[24–26] but also lower white blood cell counts.[27] In a recent study, it was shown that in patients on combination therapy, even if the 6TGN levels associated with favorable outcome were lower than when purines are used as monotherapy, a minimal dosage still was important.[28] The predictive value of a relatively low blood hemoglobin concentration is more intriguing. It has been associated with short-term relapse in several studies including the STORI trial,[9,29] and was assumed to reflect ongoing disease activity. The predictors found in the present study are slightly different from the original STORI trial. This is because failure in the 2 studies was defined differently: short-term relapse in the initial study vs long-term treatment failure or complication in the present study. Fecal calprotectin, increased CRP level, and endoscopic activity are probably more reliable markers of ongoing disease activity, and thus less relevant to predict long-term outcomes, although this conclusion should be taken with caution because one quarter of fecal calprotectin values were missing. Based on the multivariable analysis of predictors of failure, we were able to generate a simple predictive model, and to identify 3 different groups of patients. A low-risk group, defined by the absence of any predictor (hemoglobin level, >12.5 g/dL; white blood cell count, <5.0 10^9/L; and upper gastrointestinal tract involvement) and accounting for 10% to 15% of the patients, had no observed major complication after a median follow-up period of 7 years and reasonably can be considered for IFX withdrawal. A high-risk group, defined by the presence of at least 2 predictors, accounting for 15% to 20% of the patients, and with an estimated major complication rate of 43.0% (range, 16.5%–69.4%) at 7 years, should not have IFX withdrawn. Finally, an intermediate-risk group, defined by the presence of 1 risk factor, accounting for 70% of the cohort, and with an estimated rate of major complications of 16.3% (range, 6.9%–25.0%) at 7 years, should have IFX withdrawal discussed on a case-by-case basis, taking into account the risk of surgical resection or complex perianal lesions.

One strength of this cohort was the homogeneity of the population. Most studies dealing with reporting on anti-TNF withdrawal after clinical remission were limited by heterogeneous populations, variable lengths of IFX treatment before discontinuation, and variable use of immunomodulators and corticosteroids. In the STORI cohort, the population was homogenous, IFX withdrawal was standardized, and the disease characteristics at the time of stopping were collected prospectively.

Our study also had several limitations. The first 13 patients of the original STORI cohort were not included. Nevertheless, the outcomes of these patients at the end of the original study were not different from the outcomes of the rest of the cohort. Second, as in the original study, there was no control group in which IFX would have been continued. Third, our patients were highly selected and can be considered as the best responders to IFX therapy because most were in clinical and endoscopic remission when the drug was stopped. Fourth, because of the retrospective collection of the data after the end of the STORI trial, the follow-up time was variable. However, only 5 patients had a follow-up time fewer than 3 years, including 3 patients whose follow-up evaluation was censored owing to start of adalimumab

instead of IFX. Fifth, because of the retrospective design of the study no objective parameters such as endoscopy could be collected and no measurement of IFX trough levels or IFX antibodies were available. Although in the initial STORI trial only 1 of 52 re-treated patients developed anti-IFX antibodies after a short-term period,[9] later anti-IFX antibody development and low trough levels could account for IFX restart failures or major complications.

In conclusion, in patients in remission on combination therapy with IFX and immunomodulators, approximately 70% of the patients did not experience a failure of the de-escalation strategy and a little less than one fifth of the cohort developed major complications 7 years after IFX withdrawal. Prospective controlled trials are needed to assess the benefits and risks of transient and prolonged biologic treatment withdrawal in CD and to validate predictors of poor outcomes after withdrawal.

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 https://doi.org/10.1016/j.cgh.2017.09.061.

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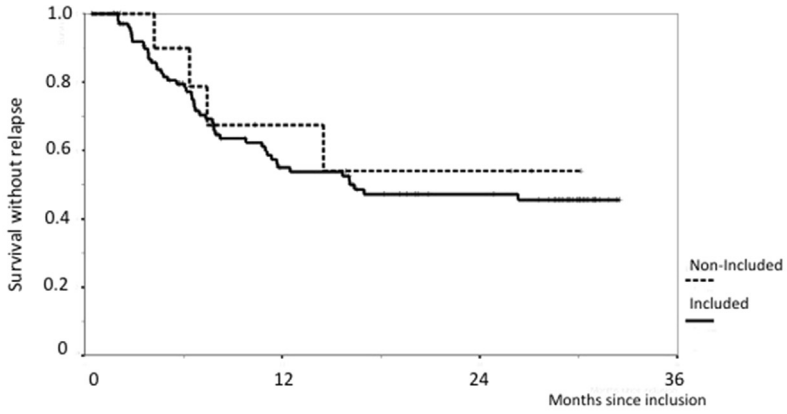
Reprint requests
Address requests for reprints to: Catherine Reenaers, MD, PhD, Gastroenterology Department, Centre Hospitalier Universitaire Liège, Avenue de l'Hôpital B35, 4000 Liège, Belgium. e-mail: catherine.reenaers@chu.ulg.ac.be; fax: (32) 4-3667889.

Conflicts of interest
These authors disclose the following: Catherine Reenaers has received consulting fees, lecture fees, and travel accommodations from AbbVie, Takeda, MSD, Mundipharma, Hospira, and Ferring; Maria Nachury has received lecture fees from Abbvie, MSD, and Ferring; Yoram Bouhnik has received consulting fees from BMS, Shire, Sanofi, Norgine Pharma, MSD, AbbVie, Astra Zeneca, Roche, Takeda Millenium, and Janssen Cilag, lecture fees from AbbVie, Falk, BMS, MSD, Ferring, Given Imaging, Mayoli-Spindler, Norgine Pharma, and Vifor Pharma, and is a shareholder of Inception IBD (San Diego, CA); David Laharie has received consulting and lecture fees from AbbVie, Ferring, Janssen Cilag, MSD, Pfizer, and Takeda; Matthieu Allez has received honoraria from Novo Nordisk, MSD, AbbVie, Ferring, Genentech, TxCell, Janssen, Pfizer, GSK, Hospira, and UCB; Mathurin Fumery has received lecture fees from Abbvie, MSD, and Ferring; Aurelien Amiot has received consulting fees from AbbVie, Takeda, and Biocodex, lecture fees and travel accommodations from AbbVie, Biocodex, and MSD, and advisory board fees from Gilead, Takeda, and AbbVie; Guillaume Savoye has received lecture fees from Vifor, HAC Pharma, AbbVie, MSD, and Ferring France, travel accommodations from Ferring, AbbVie, and MSD France, and a research grant from Ferring; Martine Devos, Georgia Malamut, Arnaud Bourreille, and Bernard Flourie have received board and lecture fees from Abbvie, Ferring, Janssen, MSD, Norgine, and Takeda; Philippe Marteau and Lucine Vuitton have received lecture fees from AbbVie, MSD, Takeda, Norgine, and Ferring, and consulting fees from AbbVie and Takeda; Stephanie Viennot has received consulting fees from AbbVie, MSD, Takeda, Vifor Pharma, and Ferring; Jean-Frédéric Colombel has served as a consultant or advisory board member for Abbvie, ABScience, Amgen, Bristol Meyers Squibb, Celltrion, Danone, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen, Immune Pharmaceuticals, Medimmune, Merck & Co, Millenium Pharmaceuticals, Inc, Neovacs, Nutrition Science Partners Ltd, Pfizer, Inc, Prometheus Laboratories, Protagonist, Receptos, Sanofi, Schering Plough Corporation, Second Genome, Shire, Takeda, Teva Pharmaceuticals, Tigenix, UCB Pharma, and Vertex; and Edouard Louis has received fees for research grants from AstraZeneca, Schering-Plough, and Abbott, speaker fees from Abbott, Abbvie, AstraZeneca, Ferring, Schering-Plough, MSD, Chiesi, Menarini, Nycomed, Falk, and UCB, has served on the advisory board for Abbott, Abbvie, Ferring, UCB, MSD, Millenium, Mitsubishi Pharma, and Takeda, and as a consultant for Abbvie.

The remaining authors disclose no conflicts.



Included patients	Follow-up time ±SE (months)	Number of relapses/ number of patients	Proportion of relapse at 1 year (%) ±SE	Proportion of relapse at 2 years (%) ±SE	P Log rank	Hazard ratio estimate (95% CI)
yes	28.6±0.8	48/102	45.0±5.3	52.7±5.4	0.64	1.0
No	15.9±6.5	4/13	32.5±15.5	44.0±17.3		0.79 (0.28-2.18)

CI: Confidence Interval

Supplementary Figure 1. Survival without relapse curve in the STORI trial for the patients secondarily included vs nonincluded in the STORI long-term study. At the end of the initial STORI trial the patients' survival without relapse was not statistically different in the subgroup of included vs nonincluded patients.

Supplementary Table 1. Baseline Characteristics of the Patients Secondarily Included vs Nonincluded in STORI Long-Term Study

Demographic, clinical, biological, and endoscopic characteristics of patients	Participating centers (19/20); N = 102 patients, n (%) or median (IQR)	Missing center (1/20); N = 13 patients, n (%) or median (IQR)	*P* value
Male	43 (42)	6 (46)	.78[a]
Age, *y*	32 (25–39)	30 (27–39)	.93[b]
Disease duration, *y*	7 (4–12)	11 (6–15)	.12[b]
Active smoker	39 (38)	6 (46)	.58[a]
Disease site (N = 101 and 13)			
Ileal	12 (12)	2 (15)	.97[a]
Colonic	57 (56)	7 (54)	
Ileocolonic	32 (31)	4 (31)	
Upper gastrointestinal tract	9 (9)	0	.59[c]
Anoperianal lesions	37 (36)	3 (23)	.53[d]
Intestinal stricture at infliximab initiation (N = 101)	6 (6)	5 (38)	.003[c]
Intra-abdominal fistulizing disease at infliximab initiation	1 (1)	2 (15)	.033[c]
Previous surgical resection	22 (22)	3 (23)	1.00[d]
Treatment history			.21[c]
Methotrexate	17 (17)	0	
Azathioprine/mercaptopurine	85 (83)	13 (100)	
Years since infliximab initiation	2.2 (1.6–3.2)	1.5 (1.1–1.9)	.003[b]
Anti-infliximab antibody at baseline (N = 99 and 13)			.34[a]
Positive	1	0	
Negative	40	8	
Inconclusive	58	5	
Infliximab trough level	3.8 (1.8–8.2)	2.5 (1.6–7.3)	.31[b]
Endoscopic variable			
CDEIS	1.0 (0–3)	0 (0–0.4)	.003[b]
CDEIS = 0	31 (30)	8 (62)	.055[d]
Remaining ulcers	39 (38)	0 (13)	.04[c]
Biologic variables			
Hemoglobin level, *g/L*	136 (129–144)	129 (123–146)	.42[b]
White blood cell count, 10^9/L	6.2 (5.0–7.7)	5.4 (4.2–6.2)	.044[b]
Platelet count, 10^9/L	273 (233–312)	269 (201–319)	.69[b]
hsCRP, *mg/L* (n = 96 and 13)	2.0 (0.8–4.8)	2.5 (0.9–5.2)	.97[b]
Fecal calprotectin level, *μg/g* (n = 75 and 10)	51 (30–350)	52 (37–153)	.84[b]

CDEIS, CD Endoscopic Index of Severity; hsCRP, high-sensitivity CRP.
[a]Chi-square.
[b]Mann–Witney test.
[c]Fisher exact test.
[d]Chi-square with continuity correction.