Clinical Gastroenterology and Hepatology

LONG-TERM OUTCOME AFTER INFLIXIMAB WITHDRAWAL FOR SUSTAINED REMISSION IN CROHN'S DISEASE

--Manuscript Draft--

Manuscript Number:	CGH-D-17-00452R2
Full Title:	LONG-TERM OUTCOME AFTER INFLIXIMAB WITHDRAWAL FOR SUSTAINED REMISSION IN CROHN'S DISEASE
Article Type:	Clinical - Alimentary Tract
Section/Category:	Clinical Research (non-trial)
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Abstract:	Background & Aims: The long-term outcome of Crohn's disease patients after infliximab (IFX) withdrawal is not well established. The aim of this study was to describe the long-term outcomes of Crohn's disease patients in clinical remission after IFX treatment was withdrawn. Methods: All patients included in the Infliximab DiSconTinuation in CrOhn's disease patients in Stable Remission on Combined Therapy with Immunosuppressors (STORI) cohort were considered for inclusion (n=115, 20 GETAID centres). The following events were retrospectively recorded from the end of STORI to the last available follow-up: surgery, new complex perianal lesions (representing major complications), the need to restart a biologic and and IFX restart failure (defined as non-response, secondary loss of response, IFX-related side-effects leading to IFX interruption). De-escalation strategy failed when a major complication or IFX restart failure occurred. Results: 102/115 STORI patients from 19/20 GETAID centres were included. The median follow-up time was about 7 years. 21.6% (95%CI: 13.1-30.3) of the patients did not restart a biologic treatment and did not have a major complication 7 years after IFX withdrawal. Among patients who restarted IFX, 30.1% (95% CI: 18.5-42.5) experienced a failure of the strategy 6 years after restarting. Overall, at 7 years, major complications occurred in 18.5% (95%CI: 10.2-26.8) while 70.2% (95%CI: 60.2-80.1) had no failure of the de-escalation strategy. The factors independently associated with major complications were an upper-gastrointestinal disease location, white blood cell count ≥ 5.0 109/l, and hemoglobin ≤ 12.5 g/dl at the time of IFX withdrawal. Patients with at least 2 factors had a risk > 40% of having a major complication in the 7 years following IFX withdrawal. Conclusions: In the long-term follow-up of the STORI cohort (7 years), while only one fifth of the patients did not restart biologic therapy and did not develop major complications, stopping IFX may be considered as a successful strategy in 70% of patients.

Liège, September 2nd 2017

Dear Editor,

Please find enclosed the second revisison of our manuscript entitled "Long-term outcome after Infliximab withdrawal for sustained remission in Crohn's disease" to be submitted for publication in Clinical Gastroenterology and Hepatology.

All the questions from the second reviewer have been answered and the suggestions have been taken into account. New statistics have been performed on the 13 non-included patients. Supplementary table 1 and supplementary figure 1 have been added for more clarity.

We thus hope that this manuscript will be suitable for publication in Clinical Gastroenterology and Hepatology.

This manuscript has not been previously published and is not being considered currently by another journal.

The authors have no conflict of interest concerning this study.

Yours sincerely,

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Responses to reviewer 2

Comment 1:

One can't say anything about the missing 13 patients, and therefore the most conservative approach would have been more fair. It might have been that the center was not interested in the follow-up of this study since all their patients did worse after infliximab discontinuation… Can the authors give any comparative data between the baseline values and the STORI outcome data between the patients in this specific center and the others?

Answer 1:

As suggested by the reviewer, a comparison of the subgroups of patients not included versus included in STORI long-term study was performed (supplementary table 1). A higher proportion of patients with complicated disease (stricture and intra-abdominal fistulae) at infliximab initiation were observed in the subgroup of non-included patients. Median years since Infliximab was lower in the subgroup of non-included patients. The median CDEIS, as well as the proportion of patients with remaining ulcers, were lower at inclusion in the subgroup of non-included patients. Distributions of biologic data at inclusion as well as those of IFX trough levels and anti-drug antibodies were similar in both subgroups. We also compared the relapse-free survival curves at the end of STORI study between the subgroups of included and non-included patients in STORI long-term study and no difference was observed between the 2 subgroups (supplementary figure 1).

We have added a short comparison of the 2 subgroups in the results and implemented the discussion accordingly. Even if it is difficult to be sure that these differences could have an effect or not on our published results and if yes in what direction, we recognized that the non-inclusion of the 13 patients is a limitation of our study and we have highlighted this point in the discussion.

Supplementary table 1

Baseline characteristics of the patients secondarily included versus non-included in STORI-long term study.

Demographic, clinical , biological and endoscopic characteristics of the patients	Participating centres (19/20) N=102 patients n (%) or median (IQR)	Missing centre (1/20) N=13 patients n (%) or median (IQR)	P value
Male	43 (42)	6 (46)	0.78[c]
Age (years)	32 (25-39)	30 (27-39)	0.93[m]
Disease duration (years)	7 (4-12)	11 (6-15)	0.12[m]
Active smoker	39 (38)	6 (46)	0.58[c]
Disease site (N=101 and 13) Ileal Colonic Ileocolonic Upper gastro-intestinal tract	 12 (12) 57 (56) 32 (31) 9 (9)	 2 (15) 7 (54) 4 (31) 0	 0.97[c] 0.59[f]
Anoperianal lesions	37 (36)	3 (23)	0.53[cc]
Intestinal stricture at Infliximab initiation (N=101)	6 (6)	5 (38)	0.003[f]
Intra-abdominal fistulizing disease at Infliximab initiation	1 (1)	2 (15)	0.033[f]
Previous surgical resection	22 (22)	3 (23)	1.00[cc]
Treatment history Methotrexate Azathioprine/Mercaptopurine	 17 (17) 85 (83)	 0 13 (100)	0.21[f]
Years since Infliximab initiation	2.2 (1.6-3.2)	1.5 (1.1-1.9)	0.003[m]
Anti-Infliximab antibody at baseline (N=99 and 13) positive negative inconclusive	 1 40 58	 0 8 5	0.34[c]
Infliximab trough level	3.8 (1.8-8.2)	2.5 (1.6-7.3)	0.31[m]
Endoscopic variable CDEIS CDEIS=0 Remaining ulcers	 1.0 (0-3) 31 (30) 39 (38)	 0 (0-0.4) 8 (62) 0 (13)	 0.003[m] 0.055[cc] 0.04[f]
Biologic variables Haemoglobin (g/l) White blood cell count (10^9/l) Platelet count (10^9/l) hsCRP (mg/l) (n=96 and 13) Fecal calprotectin level (µg/g) (n=75 and 10)	 136 (129-144) 6.2 (5.0-7.7) 273 (233-312) 2.0 (0.8-4.8) 51 (30-350)	 129 (123-146) 5.4 (4.2-6.2) 269 (201-319) 2.5 (0.9-5.2) 52 (37-153)	 0.42[m] 0.044[m] 0.69[m] 0.97[m] 0.84[m]

[c] Chi Square

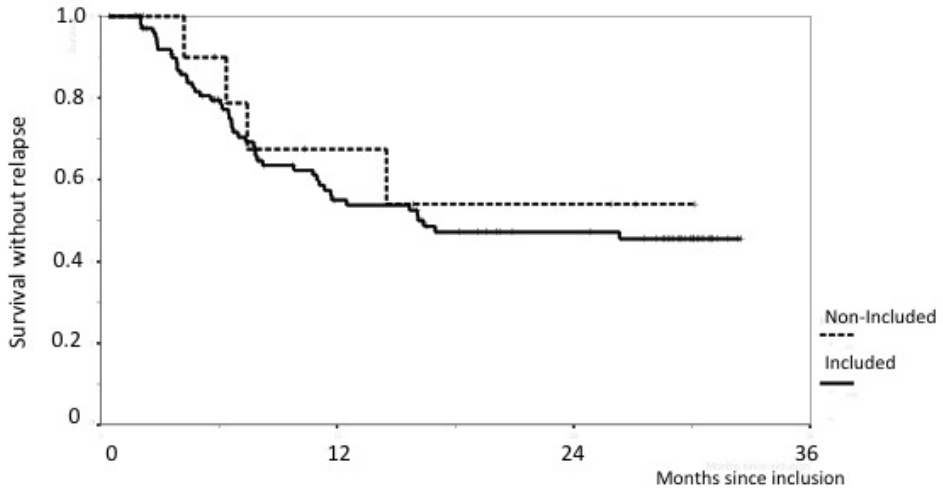
[cc] Chi Square with continuity correction

[f] Fisher exact test

[m] Mann Withney test

Supplementary figure 1

Survival without relapse in the STORI trial for the patients secondarily included versus non included in STORI long-term study



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

Comment 2:

The major finding should be that 22 out of 115 patients did not restart biological therapy or did not experience a major complication. Even more correct would be to take into account the short courses of steroids as well, leaving only 18 patient without developing a relapse requiring therapy optimization or experiencing a major complication. The rational not to present it this way remains unclear.

Answer 2:

We agree with the reviewer that this is an important result and this result is not

clearly expressed in the result section of the abstract and at the beginning of the paragraph "*Need to restart a biologic"* in the result section of the paper. As it is one of the main findings, we expressed the results as a survival rate without IFX resumption or severe complication at 7 years: "21.6% (95%CI: 13.1-30.3) of the patients did not restart a biologic treatment and did not have a major complication after 7 years". Expressing the results as "22 out of 102 patients did not restart a biological treatment and do not experienced a major complication" might be erroneously translated as a percentage by most readers. Indeed, this is not exact for 2 reasons: first this raw proportion does not take into account that the follow-up time is variable across patients, as in any cohort; second the proportion of patients who did not restart a biological treatment and do not experienced a major complication is variable with time and has to be associated with a time after IFX withdrawal.

As far as corticosteroid intake, we respectfully disagree with the reviewer's proposal to consider a short course of steroids as a failure of the strategy. This is often done in clinical practice for patients experiencing minor symptoms with no need to restart or switch to another biologic. These intakes are even sometimes decided by the patient him/herself and are note always justified.

Finally, even if we do agree that this result on 22 patients is an important result, it appears to us as not the most important one. Indeed, everybody acknowledge that there is currently no cure of CD and that stopping a drug will rarely be a long term valid option for a patient. Nevertheless, we consider that having periods off biologics may have important repercussion on the cost and the safety of CD management. Therefore it seems to us a very relevant conclusion to show that such transient biologic treatment withdrawal may be done without further loss of response to this drug and without significant intestinal damage progression in the large majority of the patients.

Comments 3:

Again, it is unclear to me why hospitalization for a flare is not regarded as a major complication

Answer 3 :

We agree with the reviewer that hospitalisation is usually considered as a serious adverse event in clinical trials in which safety issues represent one of the major

concerns. However, in our clinical follow-up study in which we aimed at defining major complication by the progression of the intestinal damage, including all the hospitalisations as major complications regardless of the hospitalisation's reason and of the following events was not considered as appropriate. Indeed classifying hospitalization as a major complication would have lead to classify the same way and at the same time: first an hospitalised patient who resumed infliximab and experienced no infliximab failure, surgery or new complex perianal disease before the end of the follow-up, second an hospitalised patient who resumed infliximab and later experienced a secondary IFX failure but no surgery or complex perianal disease afterwards, third an hospitalised patient who resumed IFX and later had to undergo surgical intestinal resection. Clearly, this is not tenable. It means that hospitalisation in our study is not an event, but that the cause of hospitalisation and the events occurring after hospitalisation are the events of interest. Also a "flare" (leading to a hospitalisation) is something difficult to assess and to use in a retrospective study as it is not defined by strict criteria. To further illustrate and document this, we reviewed the data from the 7 patients who were hospitalized without being considered as a major complication:

- Five patients were briefly hospitalised for a "flare" after IFX resumption and another biologic was started during the hospitalisation. These patients were considered as need to restart IFX at the time of IFX resumption before hospitalisation and later as a secondary IFX failure at the time of the new biologic initiation during the hospitalisation and did not experienced a major complication during follow-up.

- 1 patient still not on infliximab was hospitalised for a "flare", resumed IFX during the hospitalisation and was in clinical remission on IFX at the end of the follow-up. This patient was considered as need to restart IFX at the time of IFX resumption during the hospitalisation and did not experience another event during follow-up.

- 1 patient was hospitalised briefly while on IFX without secondary modification of treatment and was in clinical remission on IFX at the end of the follow-up. This patient was considered as need to restart IFX at the time of IFX resumption before hospitalisation and did not experienced another event during follow-up.

It is clear that, according to our study objectives, all these patients cannot be classified as a major complication at the time of hospitalisation.

Comment 4 :

The fact that more objective parameters are missing on the long-term is a major limitation

Answer 4 :

We agree with the reviewer. Unfortunately due to the retrospective design of the study we were not able to collect objective parameters in the followed patients.

This limitation is acknowledged in the discussion.

Comment 5 :

The work by Thomsen et al is publically available

Answer 5 :

Agree although just in abstract form to the best of our knowledge. It has been included (reference 18).

Comment 6 :

The authors are not able to convince us about the value of their model if 70% of the patients remain in the "grey zone"

Answer 6 :

We respectfully disagree with the reviewer since in clinical practice the value of a model is not mainly linked to the size of the groups that it defines but rather by the strength and the relevance of the information that it provides for at least a subgroup of patients. The ideal situation would of course be to have clear information for each individual patient but in practice, this is rarely achieved. The model we propose allows to suggest that in the subgroup of patients having two risk factors there is a >40% risk of major complication over the follow up. We consider this risk high enough to definitely discourage treatment withdrawal in this situation. Even if it concerns only 15%-20% of the patients, we consider it as an useful and relevant information.

LONG-TERM OUTCOME AFTER INFLIXIMAB WITHDRAWAL FOR SUSTAINED REMISSION IN CROHN'S DISEASE

Short title: Infliximab withdrawal in Crohn's disease

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Abbreviations:

6TGN: 6-thioguanine nucleotides

ATI: anti-IFX antibodies

CD : Crohn's Disease

CDAI: CD activity index

CDEIS: CD Endoscopic Index of Severity

CI: confidence interval

GETAID: Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif

hsCRP: high-sensitivity C-reactive protein

HR: Hazard Ratio

IFX : Infliximab

IQR: interquartile range

STORI : infliximab di**S**con**T**inuation in Cr**O**hn's disease patients in stable **R**emission on combined therapy with **I**mmunosuppressors

TNF: Tumor Necrosis Factor

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Disclosures:

Catherine Reenaers has received consulting fees, lecture fees and travel accomodations from AbbVie, Takeda, MSD, Mundipharma, Hospira, 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 ; Bernard Flourie has received board and lecture fees from Abbvie, Ferring, Janssen, MSD, Norgine, and Takeda.; Philippe Marteau ;

Lucine Vuitton has 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 served as 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, Vertex ; Edouard Louis received fees for research grant from AstraZeneca, Schering-Plough, Abbott; speaker fees from Abbott, Abbvie, AstraZeneca, Ferring, Schering-Plough, MSD, Chiesi, Menarini, Nycomed, Falk, UCB; advisory board for Abbott, Abbvie, Ferring, UCB, MSD, Millenium, Mitsubishi Pharma, Takeda; consultant for Abbvie.

The remaining authors disclose no conflicts.

Author contributions:

Catherine Reenaers: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript

Jean-Yves Mary : study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, statistical analysis

Jean-Frederic Colombel : analysis and interpretation of data, critical revision of the manuscript for important intellectual content

Edouard Louis : study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

Jérôme Lambert: statistical analysis

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: acquisition of data

Abstract:

Background & Aims: The long-term outcome of Crohn's disease patients after infliximab (IFX) withdrawal is not well established. The aim of this study was to describe the long-term outcomes of Crohn's disease patients in clinical remission after IFX treatment was withdrawn.

Methods: All patients included in the Infliximab Di**S**con**T**inuation in Cr**O**hn's disease patients in Stable **R**emission on Combined Therapy with **I**mmunosuppressors (STORI) cohort were considered for inclusion (n=115, 20 GETAID centres). The following events were retrospectively recorded from the end of STORI to the last available follow-up: surgery, new complex perianal lesions (representing major complications), the need to restart a biologic and and IFX restart failure (defined as non-response, secondary loss of response, IFX-related side-effects leading to IFX interruption). De-escalation strategy failed when a major complication or IFX restart failure occurred.

Results: 102/115 STORI patients from 19/20 GETAID centres were included. The median follow-up time was about 7 years. 21.6% (95%CI: 13.1-30.3) of the patients did not restart a biologic treatment and did not have a major complication 7 years after IFX withdrawal. Among patients who restarted IFX, 30.1% (95% CI: 18.5-42.5) experienced a failure of the strategy 6 years after restarting. Overall, at 7 years, major complications occurred in 18.5% (95%CI: 10.2-26.8) while 70.2% (95%CI: 60.2-80.1) had no failure of the de-escalation strategy. The factors independently associated with major complications were an upper-gastrointestinal disease location, white blood cell count ≥ 5.0 10^9/l, and hemoglobin ≤ 12.5 g/dl at the time of IFX withdrawal. Patients with at least 2 factors had a risk > 40% of having a major complication in the 7 years following IFX withdrawal.

Conclusions: In the long-term follow-up of the STORI cohort (7 years), while only one

fifth of the patients did not restart biologic therapy and did not develop major complications, stopping IFX may be considered as a successful strategy in 70% of patients.

Key Words: Crohn's disease; IFX withdrawal; major complication; successful IFX restart

Background

Therapeutic strategies in Crohn's disease (CD) have evolved considerably in the past few decades. The recognition that subclinical and under-treated 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 following 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 STORI trial[9] (infliximab di**S**con**T**inuation in Cr**O**hn's disease patients in stable **R**emission on combined therapy with **I**mmunosuppressors) was the first prospective study in CD looking at the risk and predictors of relapse following 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%) in clinical response. Several withdrawal studies have been published since 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 are still 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 multicentre cohort conducted in 20 centres in France and Belgium between March 2006 and December 2009. One hundred and fifteen 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 prospectively followed. Baseline clinical and demographic characteristics were prospectively collected at the time of IFX withdrawal. Clinical index, endoscopic index and biologic data were also prospectively collected at the time of withdrawal including CD activity index (CDAI), CD Endoscopic Index of Severity (CDEIS), hemoglobin, hematocrit, white blood cell count, platelet count, erythrocyte 6-thioguanine nucleotides (6TGN) (in patients treated with purine analogues), high-sensitivity C-reactive protein (hsCRP), IFX trough levels, anti-infliximab antibodies, and fecal calprotectin levels. During the STORI study follow-up, relapse was defined as a CDAI increase above 250 or >150 over two consecutive visits with a differential of at least 70 points from baseline. IFX was subsequently 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 retrospectively recorded by reviewing the clinical notes of the patients

through the last available follow-up. 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 due to either non-response, loss of response, or remission.

Outcomes

Three types of outcomes were observed: 1) need to restart IFX or any biologic, (2) IFX restart failure (3) major complication. Either of the second two outcomes was considered to be a failure of the de-escalation strategy. IFX restart failure was defined as cessation of IFX due to an acute or delayed infusion reaction, to either non-response 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/Cardiff classification[11], before or after IFX resumption.

Follow-up

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

reason (e.g. patient or doctor preference) had their follow-up 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 median (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% confidence intervals (CI), number of events, number of major complications, and number of patients at risk at pre-specified time points after IFX withdrawal. For major complications or for strategy failure, time-to-event curves were derived through the Kaplan-Meier method and described using number of events/number of patients, percentages of event-free survival with 95% CIs, and number of patients at risk at pre-specified 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 two or three classes as in the STORI study. After univariable analysis, all variables with a p value of less than 0.30 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 (HR) with 95% CI. The proportionality assumption was graphically checked.

Results

Study population

One hundred and fifteen patients recruited at 20 GETAID centres were initially included in the STORI cohort.[9] All the centres but one agreed to participate in this long-

term follow-up cohort of 102 patients. Thirteen patients from one centre 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 CDEIS scores (median, 1.0; range, 0-3), hsCRP levels (median, 2.0; range, 0.8-4.8, n=96) and fecal calprotectin (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 displayed relative to the study sample in Supplementary Table 1 and Supplementary Figure 1.

Patients follow-up

The median follow-up time was 83 months (IQR 71-93). 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). Overall 21.6% (95%CI:13.1-30.3) of patients did not restart a biologic and did not have a major complication at seven 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).

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

restarting a biologic is described in Figure 2.

Outcome after IFX resumption and IFX restart failure

Among the 64 patients who restarted IFX, 33 patients continued IFX for a median of 70 months (IQR 47-83). Seven patients successfully stopped IFX a second time after a median IFX treatment time of 41 months and were followed without treatment for a median time of 28 months. Two patients resumed IFX without failure, and were then electively 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). 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 had a major complication after a median time of 38 months and 18 (including one 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), with 6 later experiencing a major complication after a median treatment time of 23 months. The cumulative incidence of IFX restart failure is 30.1% (95%CI: 18.5-42.5) 6 years after IFX resumption and is described in Figure 3.

Major complications

Eighteen out of 102 patients experienced a major complication after a median time of 50 months (IQR 41-73) from IFX cessation including 14 surgeries and 4 new complex perianal lesions. Among the operated patients 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 following 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 ≥ 5.0 10^9/l and a hemoglobin concentration ≤ 12.5 g/dl at the time of IFX withdrawal (Table 3). A model based on the presence or absence of each of the three predictors divided the patients in three risk groups: a low risk group (defined by the absence of all three 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% (6.9-25.0) at 7 years, and a high risk group (defined by the presence of at least two predictors) of 17 patients with a rate of major complications of 43.0% (16.5-69.4) at 7 years.

Discussion

After a median follow-up time of about 7 years in patients of the STORI cohort the mains findings are the followings: about 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, a little less than one fifth required an operation or developed a complex perianal fistula.

In most studies reporting the outcome of patients with CD after IFX withdrawal the median follow-up was 1 to 2 years and they reported similar relapse rates to the STORI trial (around 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%) ten years after the last IFX infusion.[14] A French retrospective cohort comparing the outcome of CD patients after IFX 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 of 47 months in

both groups.[16] A retrospective study from Leuven[17] reported the lowest rates of CD relapse after IFX discontinuation while in clinical remission with 96%, 93% and 52% without clinical relapse after 1, 2, and 10 years, respectively. The IFX regimen was heterogeneous in this cohort with 65% receiving episodic treatment. Patients were also electively selected 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 prior to stopping IFX. [18]

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 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] demonstrated 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 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 ≤12.5 g/dl and a white blood cell count ≥ 5.0 10^9/l at the time of IFX withdrawal were each independently significantly associated with major complications after IFX cessation. These findings are consistent with the results from different population-based studies demonstrating that the presence of upper gastrointestinal involvement was strongly associated with progression toward strictures or penetrating disease[20,21] and subsequent surgery. [22,23] Meta-analyses have demonstrated 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 cells.[27] In a recent study, it was demonstrated that in patients on combination therapy, even if the 6TGN levels associated with favourable outcome were lower than when purines are used as monotherapy, a minimal dosage was still 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 due to the fact that failure in the two studies was defined differently: short-term relapse in the initial study versus long-term treatment failure or complication in the present study. Fecal calprotectin, elevated CRP 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 since 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 > 12.5 g/dl, white blood cell count < 5.0 10^9/l and upper gastro-intestinal tract involvement) and accounting for 10-15% of the patients, had no observed major complication after a median follow-up of 7 years and can be reasonably considered for IFX withdrawal. A high-risk group, defined by the presence of at least two predictors, accounting for 15-20% of the patients and with an estimated major complication rate of 43.0% (16.5-69.4) at 7 years, should not have IFX withdrawn. Finally an intermediate-risk group, defined by the presence of one risk factor, accounting for 70% of the cohort and with an estimated rate of major complications of 16.3% (6.9-25.0) at 7 years, should have IFX withdrawal discussed on a case-by-case basis, taking into account risk of surgical resection or complex perianal lesions.

One strength of this cohort is the homogeneity of the population. Most studies dealing with reporting on anti-TNF withdrawal following 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 prospectively collected.

Our study has also several limitations. First 13 patients, of the original STORI cohort were not included. Nevertheless, the outcome of these patients at the end of the original study was not different from the outcome of the rest of the cohort. Second, like 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, as most were in clinical and endoscopic remission when the

drug was stopped. Fourth, due to 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 of less than 3 years, including 3 patients whose follow-up was censored due to start of adalimumab instead of IFX. Fifth, due to 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 1/52 retreated patients developed ATI after a short-term period,[9] later ATI 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.

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Figures' legend

Figure 1: General view of patients' outcome

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), 64.4% (95%CI: 54.0-73.0) respectively 1, 3, and 5 after IFX withdrawal.

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 1, 3 and 5 years after IFX resumption.

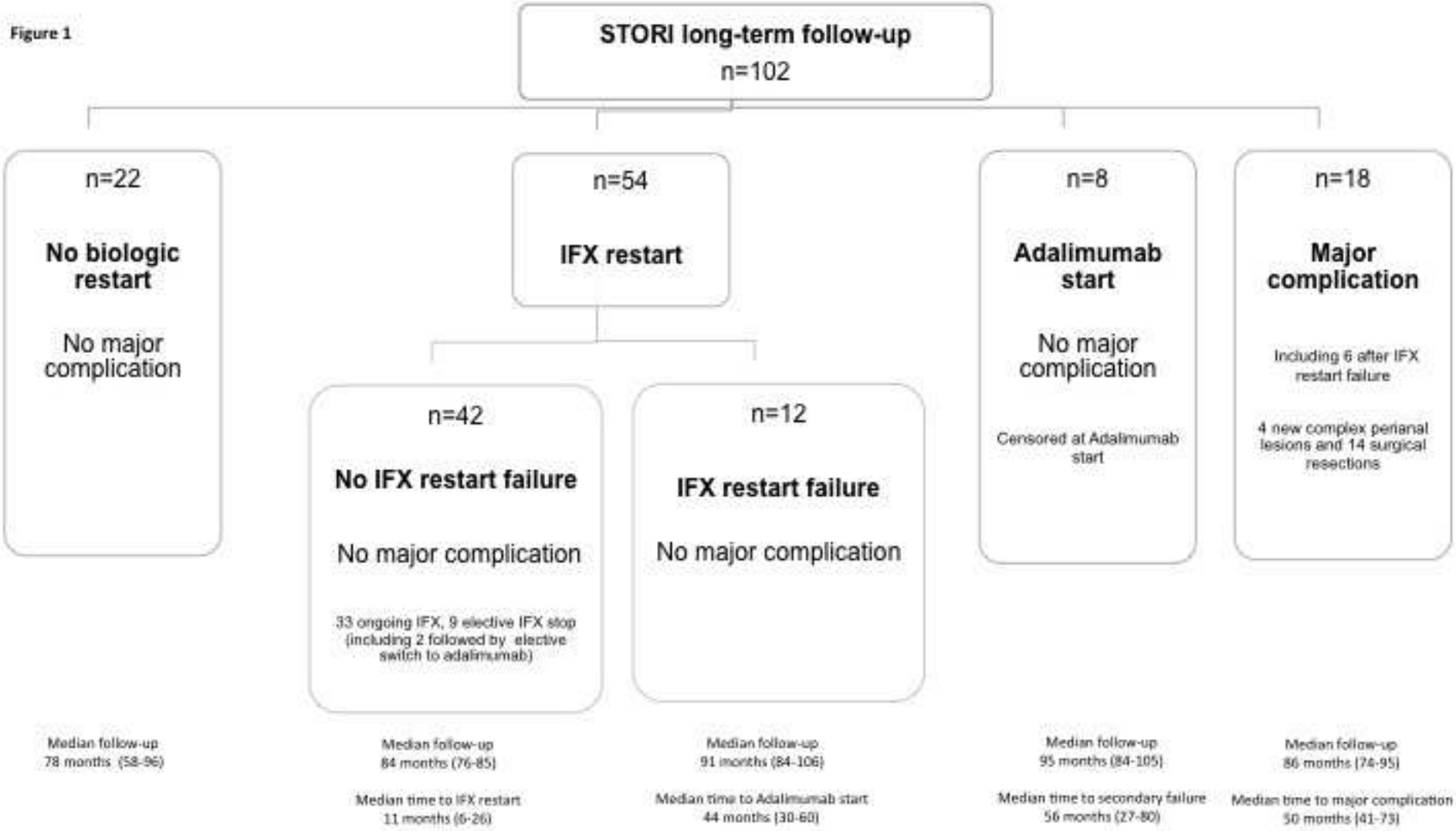
Figure 4: Kaplan-Meier survival without major complication curve.

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 1, 3, and 5 years after IFX withdrawal.

Supplementary Figure 1: Survival without relapse curve in the STORI trial for the patients secondarily included versus non-included in STORI long-term study.

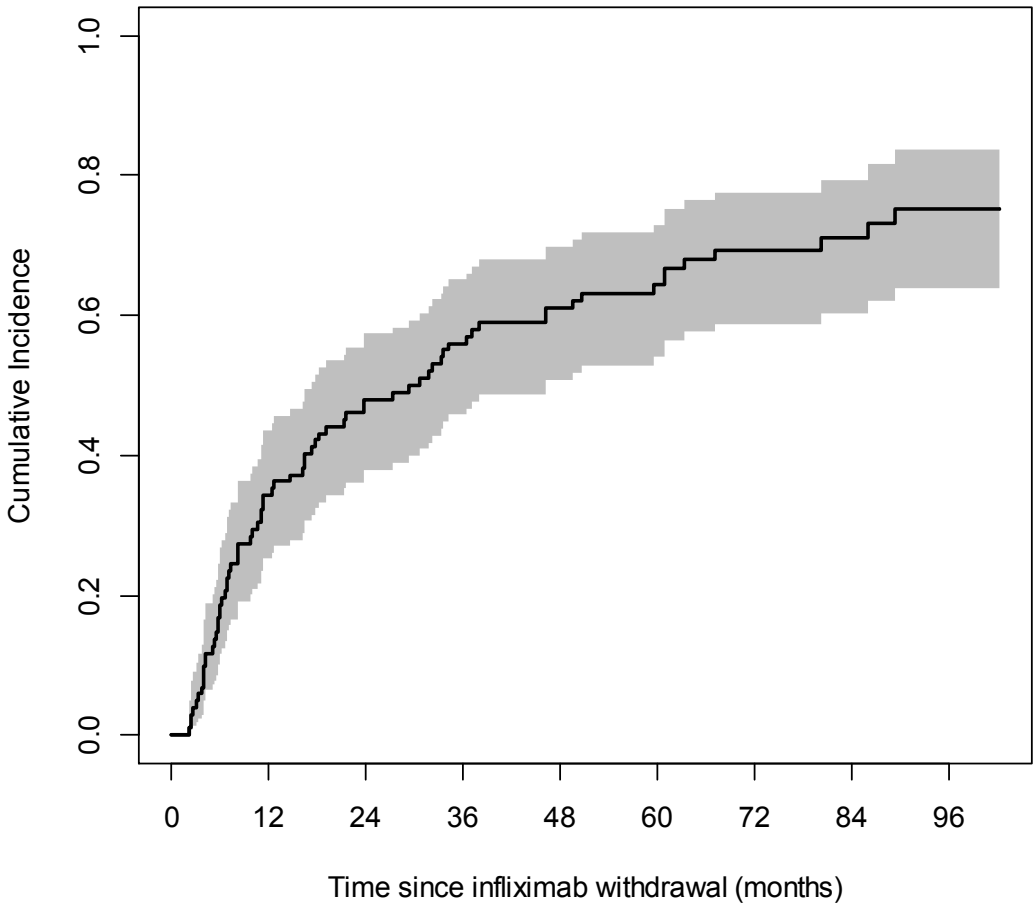
At the end of the initial STORI trial the patients' survival without relapse was not statistically different in the subgroup of included versus non-included patients.

Figure 1



Figure

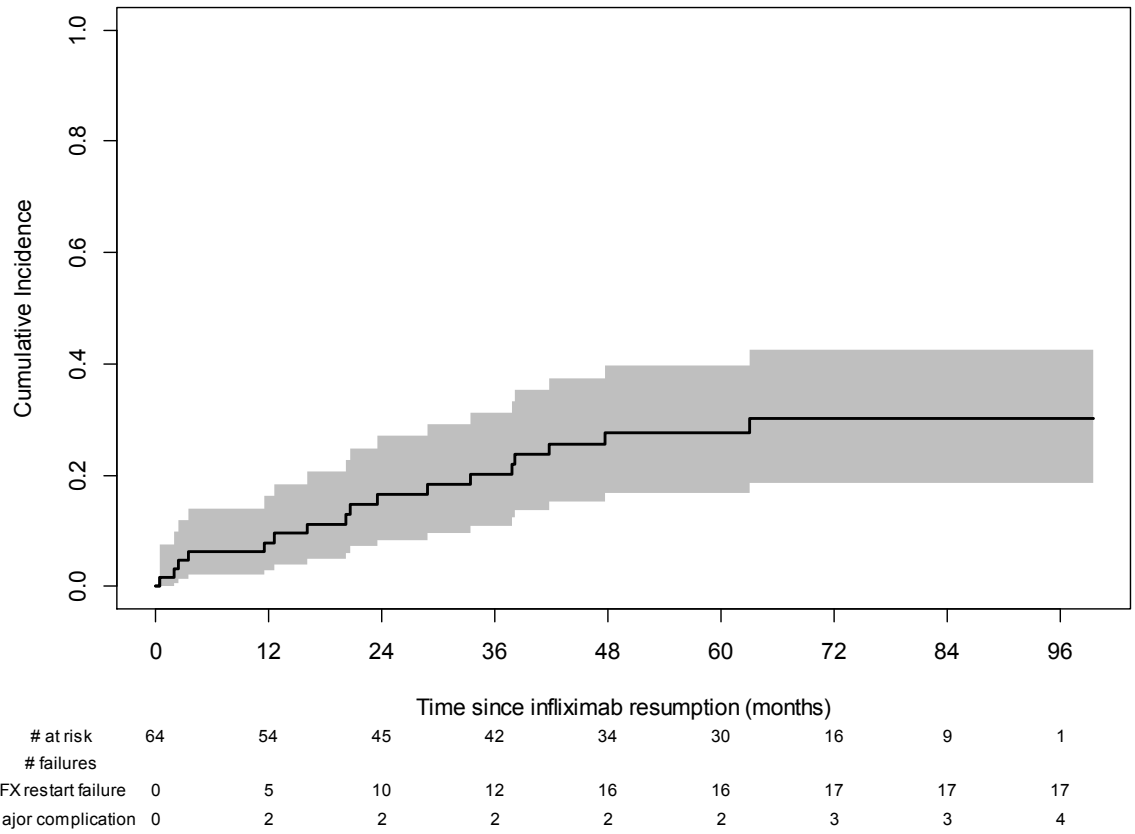
Figure 2



# at risk	102	66	51	42	32	24	18	11	3
# 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

Figure 3



# at risk	64	54	45	42	34	30	16	9	1
# 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

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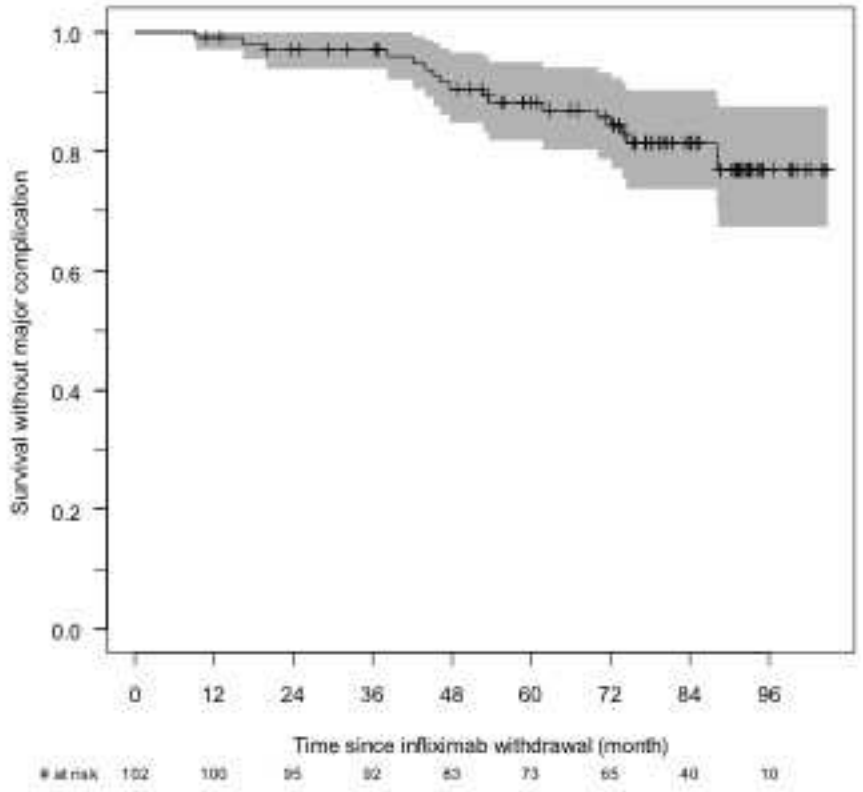
Figure 4



Figure

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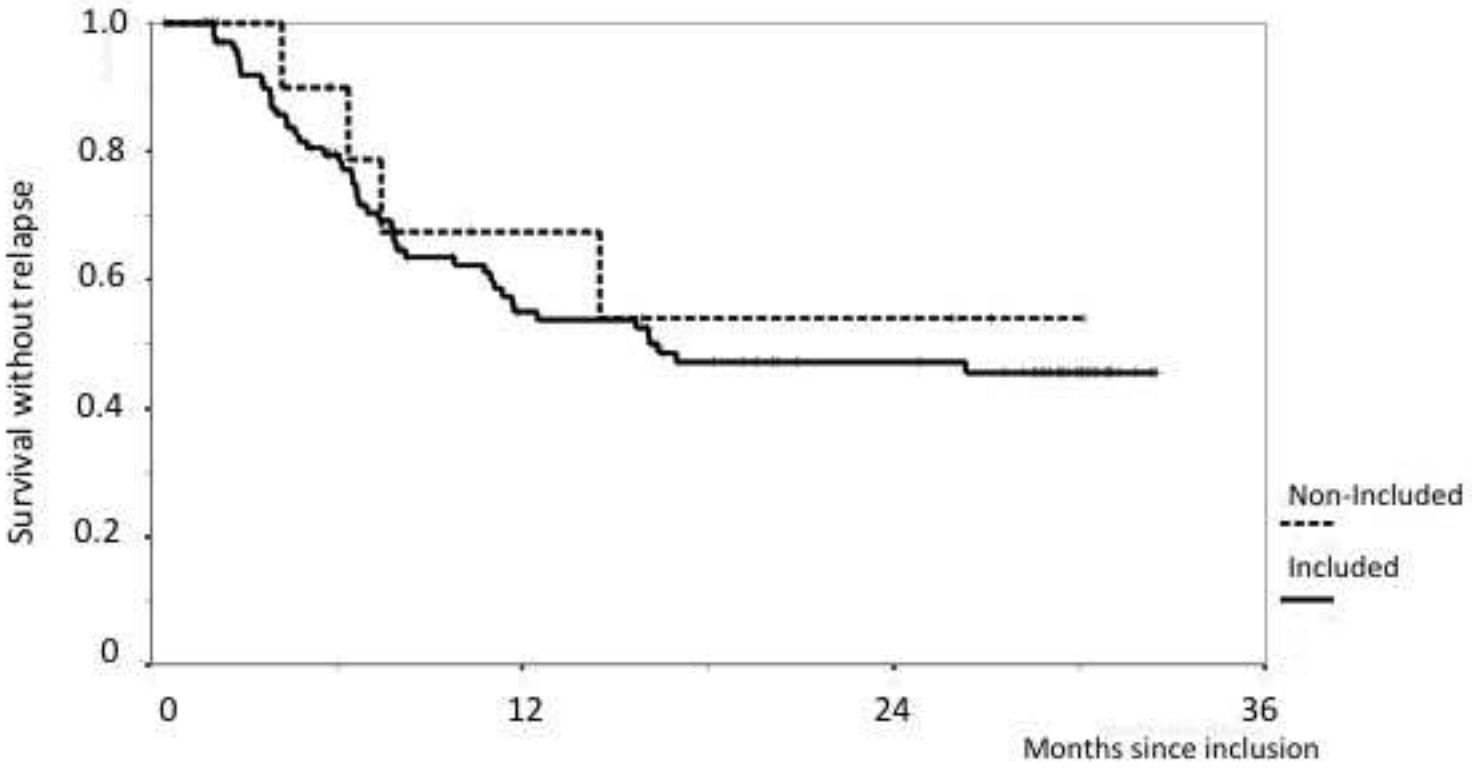

Included patients	Follow-up time ±SE (months)	Number of relapses/ number of patients	Proportion of relapse at 1 year (%) ±SE	Proportion of relapse at 2 years (%) ±SE	P Log rank	Hazard ratio estimate (95% CI)
yes	28.6±0.8	48/102	45.0±5.3	52.7±5.4	0.64	1.0
No	15.9±6.5	4/13	32.5±15.5	44.0±17.3		0.79 (0.28-2.18)

CI: Confidence Interval

Table

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 (years)	32 (25-39)
Disease duration (years)	7 (4-12)
Active smoker	39 (38)
Disease site (N=101)	
Ileal	12 (12)
Colonic	57 (56)
Ileocolonic	38 (32)
Upper gastro-intestinal 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 (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 (mg/l) (n=96)	2.0 (0.8-4.8)
Fecal calprotectin level (µg/g) (n=75)	51 (30-350)

IQR : interquartile range, CDEIS : Crohn's Disease Endoscopic Index of Severity, hsCRP : high-sensitivity C-reactive protein, N (%) or median (IQR)

Table

Table 2: Detailed outcomes of the 102 patients

IFX restart	IFX stop	Reasons of secondary IFX stop		1st event	Consequence	2nd event	Failure	
							1st event	2nd 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 complications
				surgery, n=6		none, n=5		
						complex perianal lesion, 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, =6					
			remission, n=2	none, n=7	/			
		Failure, n=4	infection, n=2	18 IFX restart failures, no major complications	none, n=4	/	4 IFX restart failures	0
			oncological issue, n=1					
			cutaneous side effect, n=1					
		Failure, n=14	loss of response, n=7		change of treatment n=14	surgery, n=3	14 IFX restart failures	6 major complications
						none, n=4		
			no response, n=1			none, n=1		
			cutaneous side effect, n=3*			surgery, n=2		
						none, n=1		
			infection, n=1			none, n=1		
			infusion reaction, n=1			none, n=1		
			myelitis, n=1			surgery, n=1		

* one occuring after the end of the study (31, December 2014)

Table

Table 3: Independant risk factors of major complication

Risk Factors	p	HR	95%CI
Upper GI tract involvement	0.027	5.8	1.5-21.8
White blood cell count ≥ 5.0 10^9/l	0.002	10.5	1.3-83.0
Hemoglobin ≤ 12.5 g/dl	0.014	4.1	1.5-21.8

GI: upper gastro-intestinal, HR: hazard ratio, CI: confidence interval

Table

Supplementary table 1

Baseline characteristics of the patients secondarily included versus non-included in STORI-long term study.

Demographic, clinical , biological and endoscopic characteristics of the patients	Participating centres (19/20) N=102 patients n (%) or median (IQR)	Missing centre (1/20) N=13 patients n (%) or median (IQR)	P value
Male	43 (42)	6 (46)	0.78[c]
Age (years)	32 (25-39)	30 (27-39)	0.93[m]
Disease duration (years)	7 (4-12)	11 (6-15)	0.12[m]
Active smoker	39 (38)	6 (46)	0.58[c]
Disease site (N=101 and 13) Ileal Colonic Ileocolonic Upper gastro-intestinal tract	 12 (12) 57 (56) 32 (31) 9 (9)	 2 (15) 7 (54) 4 (31) 0	 0.97[c] 0.59[f]
Anoperianal lesions	37 (36)	3 (23)	0.53[cc]
Intestinal stricture at Infliximab initiation (N=101)	6 (6)	5 (38)	0.003[f]
Intra-abdominal fistulizing disease at Infliximab initiation	1 (1)	2 (15)	0.033[f]
Previous surgical resection	22 (22)	3 (23)	1.00[cc]
Treatment history Methotrexate Azathioprine/Mercaptopurine	 17 (17) 85 (83)	 0 13 (100)	0.21[f]
Years since Infliximab initiation	2.2 (1.6-3.2)	1.5 (1.1-1.9)	0.003[m]
Anti-Infliximab antibody at baseline (N=99 and 13) positive negative inconclusive	 1 40 58	 0 8 5	0.34[c]
Infliximab trough level	3.8 (1.8-8.2)	2.5 (1.6-7.3)	0.31[m]
Endoscopic variable CDEIS CDEIS=0 Remaining ulcers	 1.0 (0-3) 31 (30) 39 (38)	 0 (0-0.4) 8 (62) 0 (13)	 0.003[m] 0.055[cc] 0.04[f]
Biologic variables Hemoglobin (g/l) White blood cell count (10^9/l) Platelet count (10^9/l) hsCRP (mg/l) (n=96 and 13) Fecal calprotectin level (µg/g) (n=75 and 10)	 136 (129-144) 6.2 (5.0-7.7) 273 (233-312) 2.0 (0.8-4.8) 51 (30-350)	 129 (123-146) 5.4 (4.2-6.2) 269 (201-319) 2.5 (0.9-5.2) 52 (37-153)	 0.42[m] 0.044[m] 0.69[m] 0.97[m] 0.84[m]

[c] Chi Square

[cc] Chi Square with continuity correction

[f] Fisher exact test

[m] Mann Withney test