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### ► To cite this version:

Clémence Legué, Charlène Brochard, Gregoire Bessi, Timothée Wallenhorst, Marie Dewitte, et al.. Outcomes of Perianal Fistulising Crohn's Disease Following Anti-TNF alpha Treatment Discontinuation. *Inflammatory Bowel Diseases*, 2018, 24 (6), pp.1107-1113. 10.1093/ibd/izy008 . hal-01833264

**HAL Id: hal-01833264**

**<https://univ-rennes.hal.science/hal-01833264>**

Submitted on 7 Sep 2018

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# OUTCOMES OF PERIANAL FISTULISING CROHN'S DISEASE FOLLOWING ANTI-TNF $\alpha$ TREATMENT DISCONTINUATION

**Short title:** Anti-TNF $\alpha$  discontinuation for perianal Crohn's disease

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## Source of Funding: None

**Conflicts of Interest:** GB received lecture fees from Abbvie, Ferring, MSD, Takeda and Pfizer. LS received lecture fees from Abbvie, Ferring and MSD. LS received consultant fees from Takeda and Ferring

**Author's contribution:** conception and design of the study: CL, GB acquisition of data : CL, LS, CB, MD, TW, GB; analysis and interpretation of data CL,LS, GB drafting the article or revising it critically for important intellectual content : CL GB. The manuscript was approved by all authors.

**Abbreviations:** PCD, Perianal Crohn's disease, CD; Crohn's Disease, TNF; Tumoural Necrosis Factor; AGA, American Gastroenterological Association; PDAI, Perineal Disease Activity Index; CRP, C-reactive protein; IQR, interquartile range; HR, hazard ratio; CI, confidence interval; MRI, Magnetic Resonance Imaging; CDAI, Crohn Disease Activity Index

Acknowledgment: none

## **ABSTRACT**

### **Background and aim**

Discontinuation of anti-tumour necrosis factor (TNF) $\alpha$  therapy with perianal fistulising Crohn's remains controversial due to the risk of severe relapse without any clear evidence. The aim of this study was to assess the rate and type of perianal and luminal relapses following anti-TNF $\alpha$  discontinuation.

### **Methods**

All patients treated with anti-TNF $\alpha$  for perianal fistulising Crohn's disease with subsequent discontinuation of therapy were retrospectively reviewed from a prospective database (1998-2016). Cumulative probabilities of relapse-free survival were estimated by actuarial analysis.

### **Results**

After a median follow-up of 62 months, 24 of the 45 patients experienced perianal relapse. A new surgical drainage was needed in 19 (79%) patients. The cumulative probabilities of perianal relapse at 1 and 5 years were 24% and 55%, respectively. Ileal localisation (L1) at diagnosis, persistence of an external fistula opening, second line anti-TNF $\alpha$  use or prior dose optimisation was associated with perianal relapse, whereas continuation of immunosuppressive agents decreased this risk (HR=0.3). Luminal relapse occurred in 42% of patients at 5 years. The cumulative probability of global relapse at 5 years was 67%. Retreatment with anti-TNF $\alpha$  allowed further remission in 23/24 (96%) patients.

### **Conclusion**

Half of patients with perianal fistulising Crohn's relapse within 5 years after anti-TNF $\alpha$  discontinuation. Immunosuppressant continuation may decrease this risk. The high risk of relapse (perianal and luminal) may suggest benefit in pursuing biologics over a longer period in patients with perianal fistulas

## Introduction

Perianal Crohn's disease (PCD) is observed at diagnosis in 4 to 10% of patient with Crohn's Disease (CD) and encompasses a wide variety of lesions including fistulising and non-fistulising lesions. Perianal fistulas occur in up to 37% of patients during the course of the disease<sup>1-3</sup>. Perianal involvement, especially fistulising, is the most dreaded complication of CD that leads to anal pain, faecal incontinence, dyschezia and leakage, which significantly impair quality of life and increase disability related to CD. The use of anti-tumour necrosis factor (TNF) $\alpha$  therapy has drastically changed the course of perianal fistulising disease. Infliximab was the first anti-TNF $\alpha$  used for PCD allowing induction and maintenance of fistula closure<sup>4-6</sup>. Adalimumab later showed similar efficacy<sup>7-9</sup>.

Although the efficacy of TNF antagonists was widely observed, some concerns remain regarding their long term use such as treatment cost, risk of opportunistic infections, cancer and lymphoma<sup>10-12</sup>. Due to these concerns for the long-term use of anti-TNF $\alpha$ , the top-down strategy of drug discontinuation can be implemented. On the other hand, without effective therapy, the risk of relapse remains the main issue, especially for perianal fistulising disease that could lead to new anal surgeries with subsequent anal sphincter damage, impact on quality of life and disability<sup>13</sup>. Data on luminal disease reported relapse following anti-TNF $\alpha$  discontinuation in up to half of patients after one year<sup>14-17</sup>. With that said, little is known about perianal relapse after anti-TNF $\alpha$  discontinuation and no predictors of this risk are available.

The aim of the present study was to assess the rate of fistula relapse following anti-TNF $\alpha$  discontinuation in patients treated with TNF antagonists for perianal fistulising CD and to determine factors associated with relapse.

## Patients and Methods

### Study population

The database of the University Hospital of Rennes was screened to select patients with perianal fistulising CD treated with anti-TNF $\alpha$  between 1998 and 2016. All charts of adult patients with an established diagnosis of CD, based on clinical, biological, radiologic, endoscopic and/or histological evidence, with perianal fistulising disease were reviewed.

Patients treated with at least 3 infusions of anti-TNF $\alpha$  for perianal fistulising disease who stopped the treatment because of positive perianal response, as judged by the physician, with any luminal activity of CD were included.

The following data were recorded: sex, birth date, smoking, duration of CD, CD phenotype according to the Montreal Classification<sup>18</sup>, type of fistula according to the AGA (American Gastroenterological Association) classification<sup>19</sup>, previous medications and surgical history. Regarding anti-TNF $\alpha$  treatment, the date of first and last infusions or injections and dose optimisation were recorded. In addition, concomitant medications, surgical treatment of the fistula, duration of seton drainage, abscess relapse and date of the last known event were collected. At the time of anti-TNF withdrawal, the reasons for anti-TNF $\alpha$  discontinuation, the Perineal Disease Activity Index (PDAI), the Harvey-Bradshaw score, perianal reports (ulceration, stenosis, leakage, fistula orifice), C-reactive protein (CRP) level, haemoglobin, leucocytes (polynuclear neutrophils and lymphocytes), platelets and concomitant treatment were collected, when available.

All clinical, biological and pelvic assessments were performed by experts in the field of proctology and recorded systematically in a prospective database. Patients were willing to be registered in a prospective database for research use, and the study was approved by the “Commission Nationale Informatique et Liberté” (CNIL No. 1412467).

### End Points

The primary end point was time to relapse after withdrawal of anti-TNF $\alpha$ , and the secondary end points looked for factors associated with relapse. Perianal and luminal relapses were assessed separately. Perianal relapse was defined by the recovery of leakage in patients without a draining fistula tract after anti-TNF $\alpha$  discontinuation, an abscess or the need for

surgical drainage during follow-up. Luminal relapse was defined by either an objective marker of mucosal inflammation (endoscopic or imaging) or an increase in the Harvey-Bradshaw index of at least 4 points associated with an increase in the CRP level greater than 5 mg/l.

### Statistical Analysis

Quantitative variables were described as medians and percentiles (interquartile range [IQR], 25% and 75%). Categorical variables were presented as counts and percentages of the cohort. Survival analysis was used to determine the probability of luminal and perianal relapse. The cumulative probabilities of survival without these events were estimated using the Kaplan–Meier method. The time to luminal and perianal relapse was considered to begin at the date of anti-TNF $\alpha$  discontinuation and end at the date of relapse.

To identify factors associated with perianal relapse, we only performed univariate analyses using the log-rank test. When considering the continuous variables for dichotomous analysis, a Cox proportional model was performed. Multivariate analysis was not performed due to the small size of the cohort. Statistical analyses were performed using JMP Pro 11.2 software (SAS Institute Inc., Cary, NC).

## Results

### Study population

A total of 213 patients with perianal fistulising CD were treated with anti-TNF $\alpha$ . Among them, 45 patients stopped the treatment as previously defined and thus were included in the study. The median follow-up after anti-TNF $\alpha$  discontinuation was 62 months (IQR, 34-106).

Population characteristics at diagnosis and at anti-TNF $\alpha$  discontinuation are shown in Table 1 and Table 2, respectively. Sixteen patients were male, the median age at CD diagnosis was 24 years (IQR, 17-23) and the median duration of CD was 14 years (IQR, 10-19). A total of 24 patients (53.3%) had ileocolitis at CD diagnosis according to the Montreal classification. According to the AGA classification, 28 patients (62.2%) had complex fistulas before anti-TNF $\alpha$  use. Thirty-eight patients (84.4%) previously experienced surgical drainage of the fistula. Nine patients (20%) had prior major abdominal surgery and 7 patients (15.6%) had two lines of anti-TNF $\alpha$  therapy before discontinuation. Median duration of anti-TNF $\alpha$  use before discontinuation was 17.1 months (IQR, 6-27.3), and infliximab was mainly used.

At anti-TNF $\alpha$  discontinuation, median PDAI and Harvey-Bradshaw index were 2 (IQR 0-4) and 1 (IQR, 0-2), respectively (available for 25 patients). The median CRP was 3 mg/l (IQR, 1-8) and the fistula was clinically closed in 29 patients (65.9%). Luminal disease was still active at anti-TNF $\alpha$  withdrawal for 5 patients (11.1%).

Regarding concomitant treatment, an immunosuppressant (mainly azathioprine) was used in combination with anti-TNF $\alpha$  in 34 patients. An immunosuppressant was stopped in 7 of these patients during the combination therapy and was introduced in 2 patients. Finally, immunosuppressant was continued in 29 patients following biologic discontinuation (64.5%).

The reasons for drug discontinuation were sustained clinical remission in 27 patients (60%), planned isolated infliximab induction treatment in 3 patients (6.7%); intolerance in 7 patients (15.6%), including 1 patient (2%) with skin melanoma; pregnancy in 5 patients (11.1%); and patient preference in 3 cases (6.7%).

### Outcomes after anti-TNF $\alpha$ discontinuation

#### *Perianal relapse*

Twenty-four patients (53.3%) experienced perianal relapse following anti-TNF $\alpha$  discontinuation after a median time of 25.5 months (7.3-67.9). The cumulative probabilities of

perianal relapse at 1, 2 and 5 years were 23.7% (95% CI, 14.9-35.8), 35.2% (95% CI, 24.3-47.8) and 55.2% (95% CI, 41-68.6), respectively (Figure 1). Among these 24 patients, 14 patients (58%) reported an anal abscess. Nineteen out of the 24 patients (79%) required new surgical drainage of the fistula tract, while 4 (17%) had only medical re-treatment and 1 patient (4%) had no medical or surgical re-treatment. (supplementary Figure 1)

#### *Factors associated with perianal relapse*

Ileal localisation (L1) at diagnosis (HR 4.3 [1.2-12.1]), use of a second line of anti-TNF $\alpha$  or dose optimisation prior to discontinuation (HR 4.6 [1.6-12.1]) and the presence of a persistent external opening of the fistula tract (HR 2.4 [1.1-5.2]) increased the risk of perianal relapse following biologic discontinuation. Conversely, the maintenance of immunosuppressive agents after anti-TNF $\alpha$  discontinuation decreased the risk of perianal relapse (HR 0.3 [0.12-0.75]) (Figures 2 and supplementary Table 1). Prior additional surgery for tract obturation was not associated with the risk of relapse.

#### *Luminal and global relapse*

Regarding luminal disease, 5 patients had active disease at anti-TNF $\alpha$  discontinuation and 17 additional patients (37.7%) relapsed after a median time of 21.9 months (8-46.4). Twelve out of 17 (70%) patients had an objective marker of mucosal inflammation (endoscopic or imaging) while the others had an increase in the Harvey-Bradshaw index of at least 4 points associated with an increase in the CRP level greater than 5 mg/l. The median Harvey-Bradshaw index was 5 (IQR, 4-9). Two patients (10%) ultimately required surgery. The cumulative probabilities of luminal relapse at 1, 2 and 5 years were 37.9% (95% CI, 26.4-50.9), 40.7% (95% CI, 28.7-54.1) and 44.7% (95% CI, 38.4-55.3), respectively.

Overall, 36 (80%) patients experienced either luminal or perianal relapse during follow-up. The median time to relapse for luminal or perianal disease was 14.9 months (7.1-42.9). Ten patients (22.2%) had both perianal and luminal relapses. The cumulative probabilities of relapse at 1, 2 and 5 years were 54.82% (95% CI, 42.9-66.1), 60.2% (95% CI, 47.8-71.4) and 67.4% (95% CI, 54.4-78.3), respectively (Figure 3).



### Medical re-treatment

Among the 36 patients with either luminal or perianal relapse, 24 (66.6%) patients had medical re-treatment with anti-TNF $\alpha$ . The cumulative use of anti-TNF $\alpha$  following relapse were 19.2% (95% CI, 11.2-31), 30.3% (95% CI, 20-43.1) and 51.5% (95% CI, 37.4-65.4) at 1, 2 and 5 years, respectively. The median duration between discontinuation and re-treatment was 18.6 months (7.6-30.2).

The anti-TNF $\alpha$  agent used was infliximab in 19 patients (79%) and adalimumab in 5 patients (21%). Among the 19 patients (32%) treated with infliximab, 6 patients developed side effects that led to infliximab discontinuation: One patient (17%) had an appendicular infection and one patient (17%) had a non-melanoma skin cancer; 4 patients (66%) had allergic reactions, occurring early after reintroduction for 3 of them (second, second and third infusion) and later for the fourth patient (eleventh infusion). Four out of this 6 patients were switched to adalimumab. One of the 5 patients (17%) retreated first with adalimumab had a skin side effect, ultimately leading to adalimumab discontinuation and azathioprine was started.

Overall, anti-TNF re-treatment was ultimately effective in 21/24 patients (87.5%) for some patients after a switch within the class. (supplementary Figure 1)

## Discussion

This study specifically assessed the rate of perianal fistulising relapse following TNF antagonist discontinuation, which remains poorly described in the current literature. The cumulative probabilities of fistulising relapse were 23.7% and 55.2% at 1 and 5 years, respectively. The median time to relapse was 11.9 months. Perianal relapse was severe with anal abscess in half of the cases and required perianal surgery in 80% these of cases.

In perianal fistulising CD, anti-TNF $\alpha$  withdrawal led to a high risk of relapse, with 4 out of 5 patients encountering either perianal or luminal relapse in the long-term. This high rate of relapses should make clinicians reconsider the “top down” strategy in this subgroup of patients. This study provides data on perianal relapse after biotherapy discontinuation and factors associated with it in order to assess the benefit of a potential “top-down” strategy in patients with perianal fistulising CD. Although this is a retrospective study, data were retrieved from a prospective database with a long follow-up of 62 months after anti-TNF $\alpha$  withdrawal. These results are limited by the small sample size of the cohort and did not look for independent predictor of relapse by multivariate analysis. Another limitation of the study is the long inclusion period with different strategies according to evolving guidelines and the lack of controlled arm with a selection bias due to the study design.

Due to the lack of standardised treatment strategies regarding anti-TNF use and difference in treatment strategies over time, as well as the lack of standardised pelvic magnetic resonance imaging (MRI) follow-up, it was difficult to assess the impact of fistula tract healing in this real-life cohort. Several studies demonstrated the significance of mucosal healing during luminal Crohn’s disease as a therapeutic target for sustained remission and a key factor associated with sustain remission at anti-TNF discontinuation. In comparison MRI healing of the fistula tract is probably as important. Several studies reported persistent active tracks in the short term for 70-80% of patients treated with anti-TNF while the external orifice is closed and about 40% at 18 months.<sup>20,21</sup> MRI fistula resolution is variable and slower than clinical healing, explaining the need of a long-term treatment for internal track resolution. Moreover, a small prospective study on MRI based strategy suggested that MRI fistula healing led to sustained fistula resolution, while remaining on, or stopping anti-TNF treatment.<sup>20</sup>

Little data is actually available investigating perianal relapse after discontinuation of anti-TNF $\alpha$  in fistulising CD. Perianal involvement is particularly disabling and the fear of severe

perianal relapses after anti-TNF $\alpha$  discontinuation likely explains why treatment was stopped in only 45 of the 213 patients treated for perianal fistulising CD.

A prospective study assessed clinical healing and fistula track healing on MRI in 34 patients with perianal fistulising CD following anti-TNF $\alpha$  or thalidomide treatment<sup>20</sup>. In this study, 5 patients (20%) among 26 treated with anti-TNF $\alpha$  had complete clinical and MRI healing at 6 months and maintained the response during the follow-up period. Among those patients who had complete response clinically and on MRI, only two patients discontinued anti-TNF $\alpha$  and neither relapsed at 12 and 18 months and had sustained MRI healing. This study suggested that biologics could be discontinued in case of complete fistula track healing on MRI, with a low risk of relapse. In our study, no MRI data for fistula tract healing/disappearance were available, but pelvic assessments were performed by experts in the field of proctology with systematic recording in a prospective database. Closure of the fistula tract was associated with lower risk of relapse, similarly suggesting that deep remission is needed before considering treatment discontinuation.

The reason for TNF-antagonist discontinuation in the current cohort was at the physician discretion but was mainly secondary to sustained clinical remission and intolerance/side effects. In the absence of dedicated guidelines in this field and related to the long inclusion period, the reason for discontinuation was mainly based on previous guidelines for luminal disease based on available data at this time. In this context, we found by univariate analysis, continuation of immunosuppressants after anti-TNF $\alpha$  withdrawal was associated with perianal relapse with a hazard ratio of 0.3. These results are in line with those of a prospective cohort of 34 patients treated with 3 infliximab infusions followed by maintenance therapy with methotrexate monotherapy<sup>22</sup>. This study showed a maintained perianal response at 18 months for 84% of patients after infliximab discontinuation, concordant with our results of broadly 30% of relapse at similar follow-up. Conversely, use of a second line of anti-TNF $\alpha$  or dose optimisation prior to discontinuation was associated with a high risk (HR 4.6) of perianal relapses. This result agreed with those observed in a prospective cohort of 121 patients who stopped biological therapy following remission from one year of treatment, where previous biological therapy and dose intensification during the year before discontinuation were associated with relapse.<sup>24</sup>

Luminal relapse at 1 year was observed in 14% of patients. This result differed from that observed in the prospective cohort study by Louis et al., which showed that 44% of patients relapsed after anti-TNF $\alpha$  discontinuation<sup>16</sup>. In this cohort, luminal relapse was defined by an

increase in the Crohn Disease Activity Index (CDAI) by more than 70 points between 150 and 250 points, or by a CDAI above 250. We defined luminal relapse by either increases in both Harvey Bradshaw score and CRP level or objective endoscopic or imaging markers of mucosal inflammation. This more objective and stringent criteria may explain the lower risk of luminal relapse in this cohort.

The probability of both luminal and anal relapse at 1 and 2 years after anti-TNF $\alpha$  discontinuation was 30% and 48%, respectively. Similar results were found in the cohort study by Roumeguere et al, with a global relapse at 1 year of approximately 50% after anti-TNF $\alpha$  discontinuation while methotrexate was continued <sup>22</sup>. With that said, more than two thirds of patients will relapse overtime, which questions the top-down strategy in this particular population. Perianal disease remains a known risk factor of complicated Crohn's disease leading to disabling outcomes.

Medical re-treatment with a biologic targeting TNF $\alpha$  was effective in most patients often in association with perianal surgery at relapse. Of note, some patients were switched due to intolerance at the reintroduction of anti-TNF $\alpha$ , possibly secondary to anti-drug antibody formation<sup>22</sup>, but systematic drug monitoring was not performed. Altogether, the overall efficacy of medical retreatment even after a switch within the class may suggest the efficacy of the top down strategy in a small subgroup of patients in deep remission after a first line of combination therapy with immunosuppressant continuation.

In conclusion, approximately half of patients with perianal fistulising CD relapse within 5 years after anti-TNF $\alpha$  discontinuation, which may be decreased by the continuous use of immunosuppressants. Overall, the high risk of relapse (perianal and luminal) in this particular population of CD patients with perianal disease may suggest a benefit in continuing biologics long-term.

## References

1. Lapidus A, Bernell O, Hellers G, Löfberg R. Clinical course of colorectal Crohn's disease: a 35-year follow-up study of 507 patients. *Gastroenterology*. 1998;114:1151–1160.
2. Lapidus A. Crohn's disease in Stockholm County during 1990-2001: an epidemiological update. *World J Gastroenterol*. 2006;12:75–81.
3. Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. *Gut*. 2014;63:423–432.
4. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med*. 1999;340:1398–1405.
5. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876–885.
6. Bor R, Farkas K, Bálint A, et al. [Efficacy of tumor necrosis factor-alpha inhibitors in fistulising perianal Crohn's disease]. *Orv Hetil*. 2013;154:1943–1948.
7. Colombel J-F, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52–65.
8. Colombel J-F, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut*. 2009;58:940–948.
9. Dewint P, Hansen BE, Verhey E, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). *Gut*. 2014;63:292–299.
10. van der Valk ME, Mangen M-JJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF $\alpha$  therapy: results from the COIN study. *Gut*. 2014;63:72–79.
11. Williams CJM, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor- $\alpha$  therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2014;39:447–458.

12. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc.* 2009;7:874–881.
13. Ouraghi A, Nieuviarts S, Mougenel JL, et al. [Infliximab therapy for Crohn's disease anoperineal lesions]. *Gastroenterol Clin Biol.* 2001;25:949–956.
14. Bouguen G, Siproudhis L, Gizard E, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc.* 2013;11:975–981.e1–4.
15. Sands BE, Blank MA, Patel K, van Deventer SJ, ACCENT II Study. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc.* 2004;2:912–920.
16. Louis E, Mary J-Y, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology.* 2012;142:63–70.e5; quiz e31.
17. Bortlik M, Duricova D, Machkova N, et al. Discontinuation of anti-tumor necrosis factor therapy in inflammatory bowel disease patients: a prospective observation. *Scand J Gastroenterol.* 2016;51:196–202.
18. Satsangi J, Silverberg MS, Vermeire S, Colombel J-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut.* 2006;55:749–753.
19. Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB, American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. *Gastroenterology.* 2003;125:1508–1530.
20. Ng SC, Plamondon S, Gupta A, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. *Am J Gastroenterol.* 2009;104:2973–2986.
21. Tozer P, Ng SC, Siddiqui MR, et al. Long-term MRI-guided combined anti-TNF- $\alpha$  and thiopurine therapy for Crohn's perianal fistulas *Inflamm Bowel Dis.* 2012;18:825–34

22. Roumeguère P, Bouchard D, Pigot F, et al. Combined approach with infliximab, surgery, and methotrexate in severe fistulizing anoperineal Crohn's disease: results from a prospective study. *Inflamm Bowel Dis*. 2011;17:69–76.
23. Molnár T, Lakatos PL, Farkas K, et al. Predictors of relapse in patients with Crohn's disease in remission after 1 year of biological therapy. *Aliment Pharmacol Ther*. 2013;37:225–233.
24. Lee LYW, Sanderson JD, Irving PM. Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. *Eur J Gastroenterol Hepatol*. 2012;24:1078–1085.

## Figure and Table legends

Table 1 : Baseline characteristics

Table 2: Characteristics at anti-TNF $\alpha$  withdrawal

Supplementary Table 1: Factors associated with relapse by univariate analysis (log-rang test)

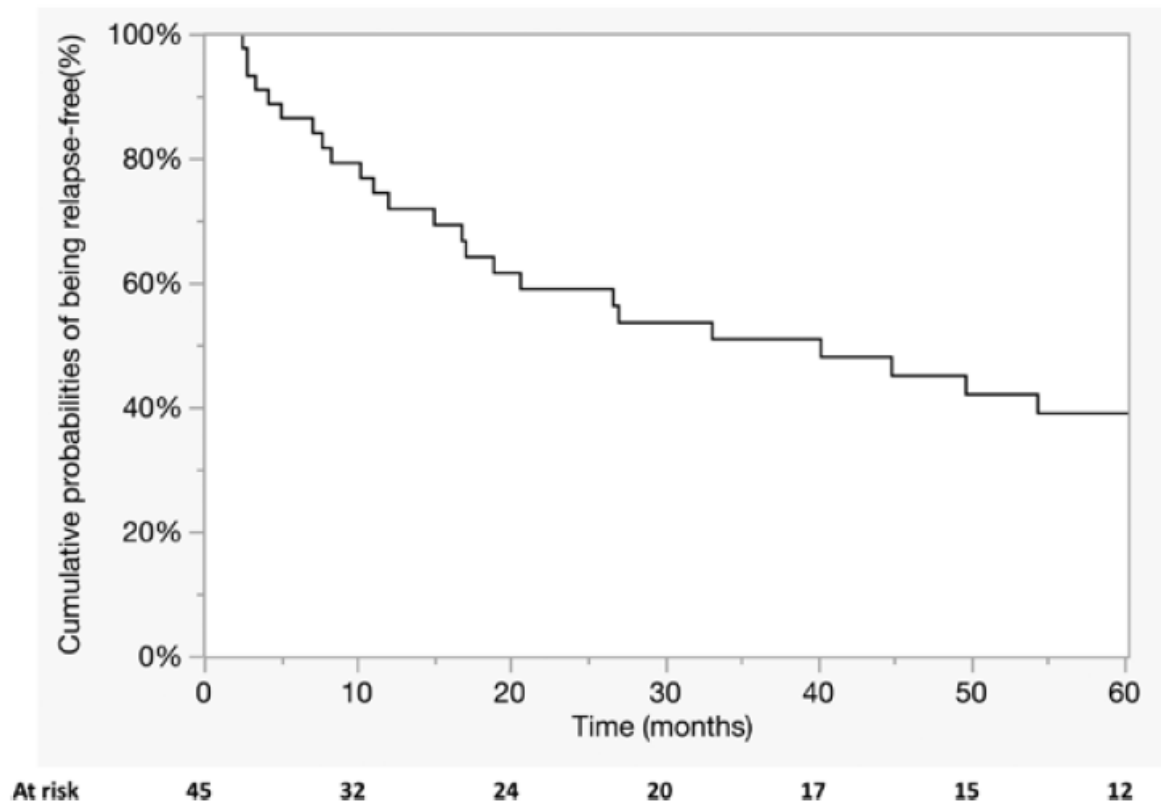


Figure 1: Cumulative probability of perianal relapse



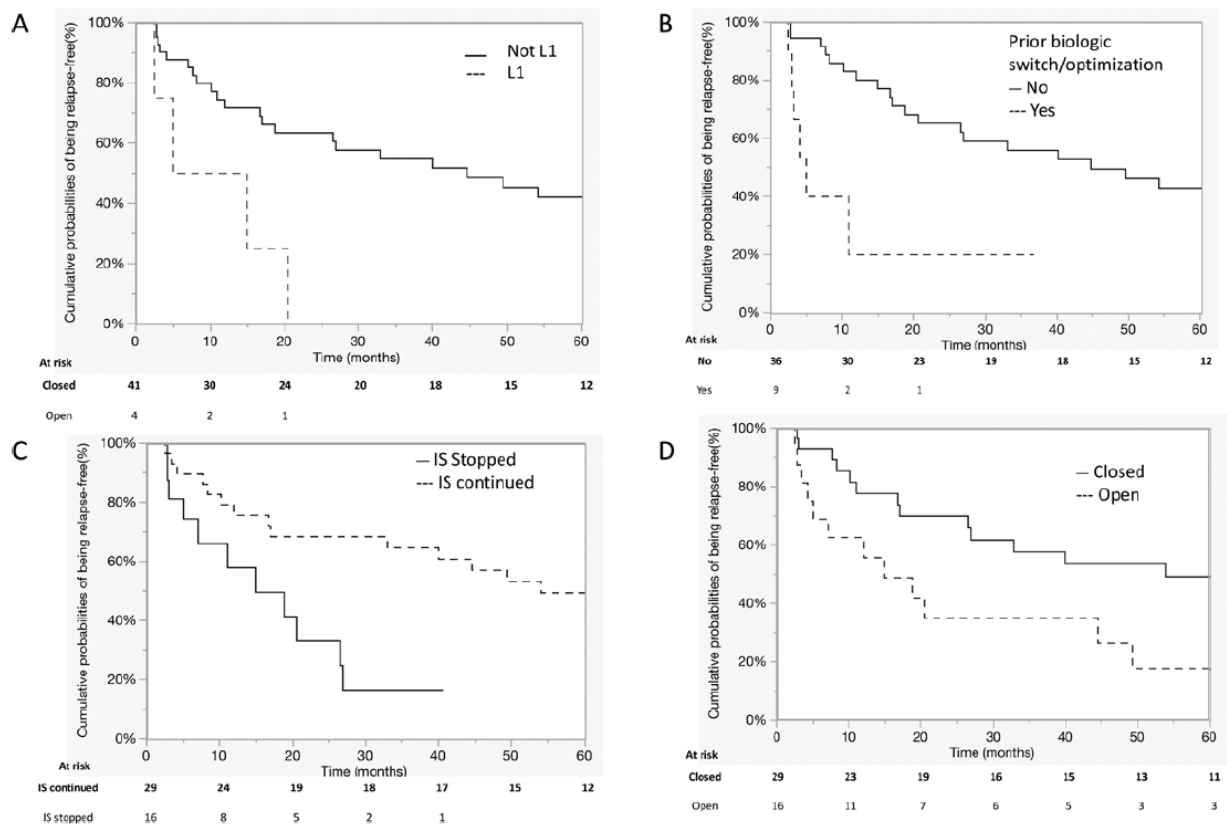


Figure 2: Factors associated with perianal relapse: ileal localisation at diagnostic (A), prior anti-TNF $\alpha$  optimisation or switch (B), pursuit of immunosuppressive agents at anti-TNF $\alpha$  withdrawal (C), the presence of an opening fistula tract. (Abbreviation: L1, iléal disease; IS, immunosuppressant)

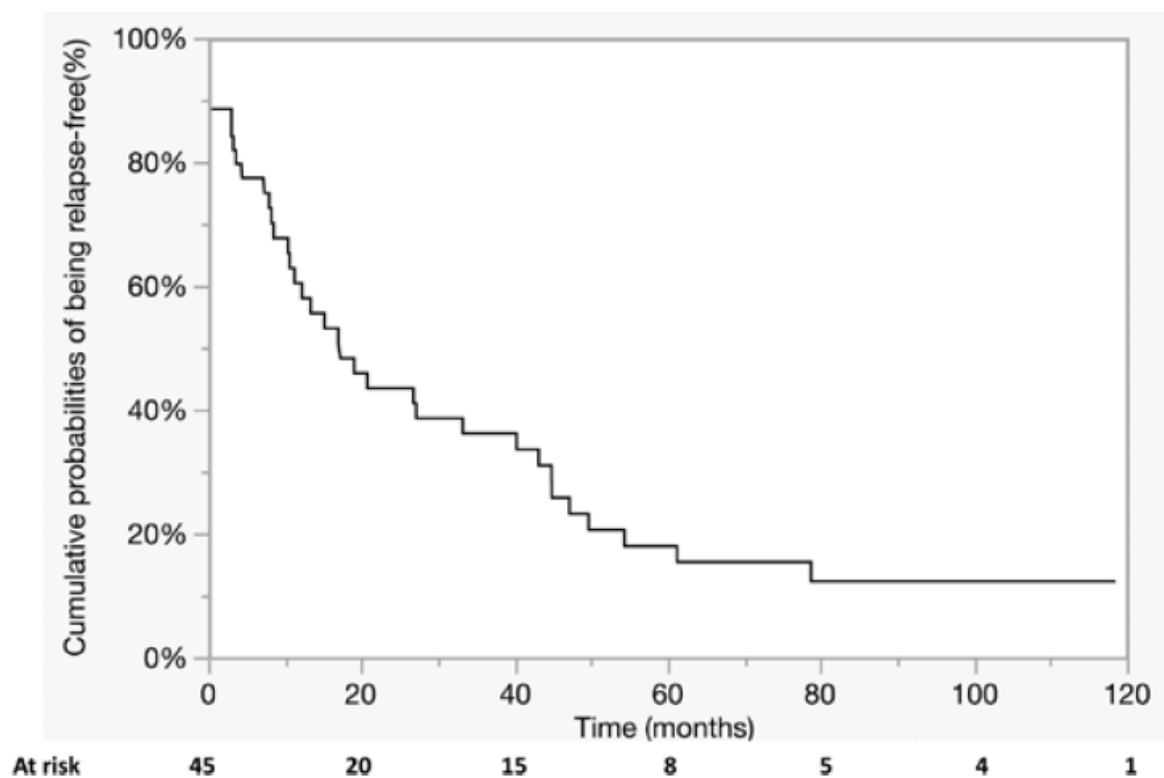


Figure 3: Cumulative probability of luminal and perianal relapse

## Supplementary Figure 1: Flow Chart

Table 1: Baseline characteristics	
VARIABLE	N = 45
Gender (M:F)	16:29
Active smoker – n (%)	11 (27)
Median disease duration – years (IQR75)	14 (10-19)
Age at CD diagnosis – years (IQR75)	24 (17-33)
Montreal classification at CD Diagnosis– n (%)	
L1 – ileal	4 (8.9)
L2 – colonic	17 (37.8)
L3 – ileo-colonic	24 (53.3)
L4 – upper digestive tract	4 (8.9)
p – perianal lesion	45 (100)
A1 – ≤ 16 years old	11 (24.4)
A2 – 17-40 years old	25 (55.6)
A3 – ≥ 40 years old	9 (20)
B1 – non-penetrating non-stricturing	29 (64.5)
B2 – stricturing	7 (15.5)
B3 – penetrating	9 (20)
Type of fistula according to the AGA classification – n (%)	
Simple	17 (37.8)
Complex	28 (62.2)
Abscess (at fistula diagnosis) – n (%)	24 (53.3)
Previous treatments – n (%)	
Prior surgery	9 (20)
Prior medical treatment	
Steroid	22 (48.9)
Immunosuppressants (AZA/6MP or MTX)	34 (75.5)
Fistula specific treatment – n (%)	
Seton – n (%)	38 (84.4)
median duration of seton – days (IQR75)	110 (0-407)
Additional surgery – n (%)	14 (31.1)
Antibiotherapy – n (%)	29 (64.4)
Stomia after anti-TNFα initiation – n (%)	1 (2.2)
Abscess after anti-TNFα initiation – n (%)	11 (24.4)
<u>Abbreviations</u> : CD, Crohn's Disease; TNF, Tumor Necrosis Factor; AGA, American Gastroenterological Association; AZA, azathioprine; 6MP, 6-mercaptopurine; MTX, methotrexate;	

Table 2 : Characteristics at anti-TNF $\alpha$ withdrawal	
Anti-TNF $\alpha$ treatment	
Duration – months (IQR75)	17.1 (6-27.3)
Two lines of anti-TNF $\alpha$	7 (15.6)
Optimization – n (%)	4 (8.9)
Infliximab (dose : 5 mg/kg) – n (%)	40 (88.9)
Regimen – n (%)	
Episodic	14 (31.1)
Episodic then scheduled	2 (4.4)
Scheduled	29 (64.4)
Number of infusions – median (IQR75)	9 (4-13)
Adalimumab (dose: 40 mg/15days) – n (%)	5 (11.1)
Associated medication – n (%)	
Steroids	9 (20)
Immunosuppressants (AZA/6MP or MTX)	34 (75.5)
Disease duration – years (IQR75)	6.4 (2.4-11.7)
Immunosuppressant continuation – n (%)	29 (64.4)
PDAI – median (IQR75) n=25	2 (0-4)
Harvey Bradshaw Index – median (IQR75) n=29	1 (0-2)
Perineal lesion – n (%)	
Ulceration	1 (2.6)
Stenosis	0 (0)
Leakage	8 (21)
Fistula closed	29 (64.4)
Biological features – median (IQR75)	
CRP (mg/l) (n=19)	3 (1-8)
Hemoglobin (g/dl) (n=17)	13.4 (11.8-14.9)
Lymphocytes ( $10^6/\text{mm}^3$ ) (n=14)	1242 (802-1846)
Neutrophils ( $10^6/\text{mm}^3$ ) (n=15)	5325 (3700-5930)
Platelet ( $10^6/\text{mm}^3$ ) (n=6)	241 (187-277)
<u>Abbreviations:</u> TNF, Tumor Necrosis Factor; AZA, azathioprine; 6MP, 6-mercaptopurine; MTX, methotrexate; PDAI, Perineal Disease Activity Index; IQR, interquartile range; CRP, C-reactive protein;	