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► **To cite this version:**

Guillaume Bouguen, Laurent Siproudhis, Emmanuel Gizard, Timothée Wallenhorst, Vincent Billioud, et al.. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab.. *Clinical Gastroenterology and Hepatology*, WB Saunders, 2013, 11 (8), pp.975-81.e1-4. 10.1016/j.cgh.2012.12.042 . inserm-00809005

**HAL Id: inserm-00809005**

**<https://www.hal.inserm.fr/inserm-00809005>**

Submitted on 23 Sep 2013

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## **Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab**

**Short title:** Infliximab for perianal Crohn's fistula

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**Grant support:** This work did not receive any financial support.

**Abbreviations used in this paper:** Tumor necrosis factor, TNF; Standard deviation, SD; Receiver operating characteristic, ROC; Inter Quartile Range, I.Q.R., perianal fistula of Crohn's disease, PCD; infliximab, IFX; Crohn's disease, CD.

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**Disclosures**

G.B., has received lecture fees from Abbott Laboratories, Ferring and MSD Pharma

L.PB. has received consulting and/or lecture fees from Merck, Abbott Laboratories and UCB  
Pharma

L.S. has received lecture fees from Abbott Laboratories and MSD Pharma

J-F.B has received lecture fees from Abbott Laboratories

V.B., E.G., M.A.B. declare no conflict of interest.

**Writing Assistance:** none

**Author contributions:** LPB and GB: study design, interpretation and analysis of data, editing of the manuscript; LS, EG, TW, VB, JFB and MAB collected data. All authors reviewed the paper and approved the final submitted draft.

## **ABSTRACT**

**Background and aims:** Long-term efficacy of infliximab in fistulizing perianal Crohn's disease is unknown. Outcomes and predictors of outcomes were evaluated in these patients.

**Methods:** The medical records of 156 patients treated with infliximab for fistulizing perianal Crohn's disease in two referral centers between 1999 and 2010 were reviewed through September 2011. Cumulative probabilities of fistula closure and recurrence were estimated using the Kaplan-Meier method. Predictors of outcomes were identified using a Cox proportional hazards model.

**Results:** At infliximab initiation, only 17.9% of patients had a simple fistula and seton drainage was performed for 97 (62%) patients. Concomitant immunosuppressants were used for 90 (56%) patients. After a median follow-up of 250 weeks, 108 (69%) patients experienced at least one fistula closure. Cumulative probabilities of first fistula closure were 40% and 65% at 1 and 5 years, respectively. Predictors of fistula closure were ileocolonic disease (HR=1.88), concomitant immunosuppressants (HR=2.58), duration of seton drainage < 34 weeks (HR=2.31) and a long duration of infliximab treatment (HR=1.76). Of the 108 patients, cumulative probabilities of first fistula recurrence were 16.6%, and 40.1% at 1 and 5 years, respectively. Forty-four (28.9%) patients developed an abscess during follow-up. A number of infliximab infusions beyond 19 was associated with less abscess recurrence (HR=0.33). At maximal follow-up, 55% of patients had fistula closure.

**Conclusions:** About two thirds of patients experienced fistula closure and one third of patients had fistula recurrence after infliximab initiation. Combination therapy, duration of seton drainage under 34 weeks and long-term infliximab treatment were associated with better outcomes.

**Keywords:** fistula, perianal disease, Crohn's disease, infliximab

## INTRODUCTION

Perianal fistulas are one of the more dreaded manifestations of Crohn's disease (CD).<sup>1</sup> Perianal disease generally denotes a more aggressive and disabling CD phenotype.<sup>2,3</sup> Patients with perianal CD (PCD) experience anal pain, discharge, dyschezia and fecal incontinence in addition to emotional symptoms and impairment of social and sexual functioning that significantly alter quality of life.<sup>4</sup> In population-based studies, perianal or rectal fistulas occur either before or after the diagnosis of CD in 13.7% to 37% of cases.<sup>3,5-8</sup>

The treatment of PCD remains a challenge in clinical practice. Before the era of biologics, 40% of patients with PCD underwent proctocolectomy.<sup>9</sup> Over the last decade, tumor necrosis factor (TNF) antagonists have changed the way of treating both luminal and fistulizing CD refractory to standard medications.<sup>10</sup> Two large placebo-controlled, randomized trials demonstrated that infliximab (IFX) is effective in inducing and maintaining fistula closure in CD.<sup>11,12</sup> Adalimumab was also significantly more effective than placebo for inducing fistula closure in a subgroup analysis of the CHARM study.<sup>13</sup> Hence, anti-TNF therapy is recommended for the treatment of complex perianal fistulas in CD.<sup>14,15</sup>

Surprisingly, data regarding the long-term outcome of perianal fistulas in patients with CD treated with IFX are scarce.<sup>16-23</sup> Due to small sample size and the relatively short follow-up of these studies, these results remain difficult to interpret.

The aim of this study was therefore to evaluate the long-term outcome of fistulizing PCD beyond one year, in a large cohort of patients treated with IFX in two French referral centers.

## **METHODS**

### **Study population**

All hospital records of consecutive adult (age > 18 years) patients treated with IFX for CD in two French referral centers (University Hospitals of Rennes and Nancy, France) between January 1998 and September 2011, were reviewed. A centralized diagnostic index was used to identify all patients with diagnosis of CD. The database of these patients with CD was then compared to the pharmacy records of all patients treated with IFX at these two hospitals. All adult patients with documented PCD at first IFX infusion and an established diagnosis of CD based on clinical, biological, radiological, endoscopic and/or histological evidence were included.

The following data were recorded: sex, birth date, age at diagnosis, CD phenotype according to the Montreal classification<sup>24</sup> at diagnosis, previous medications and history of surgery. Regarding IFX treatment, the date of first and last infusions, the number of infusions, and drug regimen for both induction and maintenance therapy were collected. IFX was administered initially at a dose of 5 mg/kg as a 2-h i.v. infusion in all patients included in this study; patients received one to three doses of IFX at weeks 0, 2 and 6 as induction therapy according to study period. Before 2003, maintenance treatment was individually tailored by the treating physician because of a lack of published data and regulatory approval defining the optimal maintenance treatment regimen. Maintenance treatment was defined as episodic (on demand) if IFX was given only upon relapse of symptoms and it was defined as scheduled if IFX was intentionally planned every 8 weeks as previously described.<sup>25</sup> Episodic treatment was also part of treatment discontinuation if patients had stopped IFX treatment for at least 4 months at maximal follow-up. Concomitant immunosuppressive medications were included in the analysis only if the total drug exposure lasted at least 3 months after IFX treatment initiation. Regarding concomitant therapy, two groups were analyzed: patients naïve to immunosuppressants (medication started after first IFX

infusion) and those with failure to immunosuppressants which were continued after IFX treatment initiation.

All patients had clinical examination under general anesthesia, associated with MRI after 2002, before starting IFX therapy according to international guidelines. Perianal fistulas were classified according to the American Gastroenterological Association (AGA) classification as either “simple” or “complex”,<sup>26</sup> and abscesses were only defined as “present” or “absent”. All patients benefited from a standardized follow-up within first year. The patients were seen by their proctologist at week 6 at third IFX infusion and then at 6 months-1 year. All proctologic reports mentioning the evolution of fistulizing perianal lesions after first IFX infusion were reviewed until last news. All perianal surgeries after IFX initiation were collected, including the presence of seton drainage.

All patients treated at University Hospitals of Rennes and Nancy for PCD benefit from a standardized follow-up by two experienced proctologists (L.S. and M.A.B.).

### **Statistical analysis**

Quantitative variables were described as median and percentile (I.Q.R. for Inter Quartile Range: 25% and 75%). Categorical variables were presented as counts and percent of the cohort. Four events were defined: (1) fistula closure was defined as the absence of any draining by fistula openings at one visit, (2) recurrence of PCD defined by the presence of fistula openings among patient who experienced fistula closure, (3) recurrence of abscess after IFX initiation, and (4) sustained fistula closure for patients without any recurrence during the follow-up after PCD healing. The events were analyzed using survival analysis. The cumulative probabilities of fistula closure, recurrence of PCD or abscess were estimated using the Kaplan Meier method. For fistula closure and recurrence of abscess, the time to healing or to recurrence was considered to begin at

the date of first IFX infusion and end at the date of complete fistula closure/recurrence of abscess or last known follow-up. For fistula, the time to recurrence was considered to begin at the date of first fistula closure and the end at the date of event or last known follow-up. To identify factors predictive of each event, we performed a univariate analysis using the log-rank test. When considering the continuous variables for dichotomous analysis, cut-off values were determined using receiver operating characteristic (ROC) analysis to reduce the risk of bias related to arbitrarily defined cut-off and identify the optimal cut-off using each outcome as a classification variable. To identify independent predictors of surgery using a multivariate analysis, all significant variables with p values of <0.05 in the log-rank test were retained in the model and integrated into a Cox proportional hazards regression model. The results are shown as HRs with 95% CIs. Statistical analyses were performed using JMP® Pro 9.0.2 software.

## **RESULTS**

### **Characteristics of the population at IFX initiation**

A total of 156 CD patients were included. The baseline characteristics at first IFX infusion are listed in Table 1. Of these patients, 61 (39%) were male (Table 1). The median age at CD diagnosis was 24 years (IQR 13-84) and the median duration of CD before IFX was 3.8 years (IQR 1-8). According to the Montreal classification,<sup>24</sup> 24 patients (15%) were diagnosed with a penetrating complication (B3) and 45% of the patients had ileo-colitis involvement (L3) at the time of diagnosis.

Baseline clinical assessment revealed complex PCD for 128 patients (82%; 95% CI 75-87), including 90 patients (58%; 95% CI 50-65) with at least one abscess. A total of 98 patients (63%; 95% CI 55-70) underwent surgery for perianal fistula. Except one patient surgically treated with fistulotomy, all surgical procedures consisted of the placement of non-cutting draining seton(s).



Fifty-one patients (36%) received immunosuppressant therapy before IFX therapy initiation and 3 patients had prior adalimumab treatment. Concomitant medications are listed in Table 1. Among the 90 patients receiving antibiotics, 27 patients had at least one abscess. A total of 105 patients were naïve to immunosuppressant. A combination therapy (IFX in association with an immunosuppressant) was started for 26 patients of these 105 patients, including 25 patients treated with thiopurine and one patient receiving methotrexate.

### **Management of perianal lesions during follow-up** (Figure 1)

After a median duration follow-up of 250 weeks (IQR 124-381), a total of 2536 IFX infusions were administered to the 156 included patients, corresponding to a median number of IFX infusions per patient of 11.5 (IQR 5-23). Induction regimen with 3 IFX infusions at week 0, 2 and 6 were performed for 151 patients. One patient had only one infusion and the 4 remaining patients had to stop IFX after the second infusion because of side effects.

Regarding maintenance IFX treatment, 42 patients (27%; 95% CI 21-34) had only episodic IFX regimen, 90 patients (58%; 95% CI 50-65) had scheduled IFX treatment with infusions every 8 weeks, and 24 patients (15%; 95% CI 11-22) had first episodic treatment before receiving scheduled IFX maintenance treatment (Table 1).

For patients undergoing a seton drainage, IFX was started after a median time of 4 weeks after surgery (IQR 0.6-18). Removal of seton was performed for 95 of 97 patients after a median duration of 33 weeks (~1.2 years; IQR 14-64). Additional surgical procedures were performed for 37 patients (24%; 95% CI 17-31), consisting of fistulotomy for 17 patients, rectal advancement flap for one patient, fibrin glue for 15 patients and anal fistula plug for 4 patients.

Anti-TNF treatment was still ongoing for 90 of the 156 patients (57%) at last news: 67 patients were still on IFX, 21 patients switched from IFX to adalimumab and 2 patients were receiving cerolizumab pegol as a third-line anti-TNF therapy. IFX treatment was discontinued after a

median duration of 86 weeks (IQR 22-201) for the following reasons: 40 patients (22%) achieved sustained clinical benefit, 21 patients (14%) were primary or secondary non-responders leading to switch to adalimumab for 20 patients, 17 patients (11%) experienced adverse events leading to switch TNF $\alpha$  antagonist for 10 patients, and 10 patients (6%) for other reasons. Finally, 72 (46%) patients achieved sustained fistula closure with IFX treatment without requiring switching to another biological agent.

### **Fistula closure**

Of the 156 patients, 108 (69%; 95% CI 61-75) had at least one complete closure of fistulas during follow-up. The median time to first fistula closure from IFX initiation was 53 weeks (~1 year; IQR 12-119). The cumulative probabilities of first clinical fistula closure at 1, 3, 5 and 10 years from the time of IFX initiation were 33%, 59%, 73% and 88%, respectively (Figure 2). At maximal follow-up, 86 (55%; 95% CI 47-63) patients had complete fistula closure.

Importantly, 72 (46%) of the 156 patients had sustained complete fistula closure throughout follow-up, including maximal follow-up. The cumulative probabilities of sustained complete fistula closure were 22%, 43%, and 57% at 1, 3, and 5 years from the time of IFX initiation, respectively.

### **Factors associated with fistula closure**

In the ROC analysis, optimal cut-off values associated with fistula closure were over 118 weeks for duration of IFX treatment, less than 34 weeks for duration of seton drainage, and less than 6 weeks between surgery and IFX initiation.

All baseline factors were evaluated in the univariate analysis using the log-rank test (See Supplementary Table 1 online). Ileocolonic disease, simple fistula, absence of draining seton,

treatment with IFX for >118 weeks as defined by ROC analysis and combination therapy were associated with fistula closure. Conversely, ileal disease, draining seton(s), long duration of inserted seton(s) over 34 weeks and long duration between surgery and IFX initiation over 6 weeks were negatively associated with fistula closure. Overall, additional surgeries (including fistulotomy, flap advancement, fibrin glue and plug) were not associated with an increased rate of fistula closure. When considering the type of additional surgery, fistulotomy but not fibrin glue was significantly associated with an increased rate of fistula closure. The other surgical procedures (flap advancement and plug) were not taking into account because of the low number of patients.

Using multivariate analysis, patients with ileocolonic disease, long-term IFX treatment over 118 weeks (2.2 years), combination therapy for patient naïve to immunosuppressant, and short draining seton(s) under 34 weeks duration were associated with first fistula closure (Table 2 and Figure 3).

Concerning sustained fistula closure, all baseline factors and treatment characteristics were first evaluated in the univariate analysis using the log-rank test (See Supplementary Table 2 online). Simple fistula, prior major abdominal surgery, absence of seton and short seton drainage duration were associated with an increased probabilities of achieving sustained fistula closure. Conversely, IFX discontinuation and a long interval period over 6 weeks between the placement of seton and the start of IFX was negatively associated with sustained fistula closure.

Using multivariate analysis, sustained fistula closure was associated with a drainage seton duration <34 weeks (HR=2.6; CI% 95 1.3-5.7 p=0.0085) and negatively associated with IFX therapy discontinuation (HR=0.18; 95% CI 0.06-0.46) (See Supplementary Table 3).

### **Recurrence of fistula and abscess**

Of the 108 patients who experienced at least one complete fistula closure, 36 (33.3%, 95% CI 25-42) had recurrence of fistula, including 24 patients with concomitant abscess. A non-cutting seton was inserted for half of patients (n=18) in case of fistula recurrence. The cumulative probabilities of first fistula recurrence were 16.6%, 31.3%, 40.1% at 1, 3 and 5 years, respectively.(See Supplementary Figure 1). When considering only the subgroup of patients treated with maintenance IFX treatment, the cumulative probabilities of first fistula recurrence were broadly similar: 12% and 36.6% at 1 and 5 years, respectively.

A total of 13 patients (9%, 95% CI 5-14) underwent proctectomy or coloproctectomy for disease refractory to IFX therapy and a stomy was performed for 2 additional patients.

Of the 156 patients 44 (29%, 95% CI 22-36) had abscess recurrence. Among them, 26 patients developed an abscess while ongoing IFX treatment and 26 patients required a new seton drainage. Of note, among the 90 patients with an abscess at time of IFX initiation, 26 patients (28.9%) had abscess recurrence.

### **Factors associated with fistula and abscess recurrence**

Using log rang test, only ileal disease was associated with fistula recurrence (See Supplementary Table 4 online). None of the baseline characteristics, including concomitant medications, were associated with fistula recurrence using multivariate analysis.

When considering abscess recurrence, IFX discontinuation and a low number of infusions (under 19 using ROC curve analysis) were associated with recurrence in univariate analysis (See Supplementary Table 5 online). Using the Cox proportional hazards regression model, only a number of IFX infusions over 19 was negatively associated with abscess recurrence (HR=0.33; 95% CI 0.13 to 0.77, p=0.0096) (Figure 4).

## DISCUSSION

This is the largest study specifically investigating the long-term outcome of perianal fistulizing CD treated with IFX, with a median follow-up of 5 years. All patients were managed by two experienced proctologists (L.S. and M.A.B.) according to international guidelines.<sup>14,15</sup>

We found that the cumulative probability of first fistula closure was 33% at one year. These results are in line with those of the ACCENT II trial that evaluated maintenance IFX treatment until at one year in fistulizing CD.<sup>12</sup> In this trial enrolling a total of 282 patients, 271 (96%) patients had perianal fistulas. Over the 54-week study, 36% of the patients had a complete absence of draining fistula, which was significantly superior to the placebo.<sup>12</sup>

Data on long-term outcome beyond one year of fistulizing PCD treated with IFX were scarce. Retrospective studies of small sample size reported that 29%, 18%, 75% and 42% of patients treated with IFX achieved sustained complete fistula closure after a median follow-up ranging from 20 to 60 months.<sup>16,18,19,22</sup> Only the group of Leuven has evaluated the long-term efficacy of IFX in fistulizing CD on a large cohort treated with IFX, but the authors did not formally analyze the outcome of perianal fistulas/abscess.<sup>25</sup>

Some studies reported a same efficacy for surgery alone and an approach combining surgery and IFX treatment.<sup>17,19,23</sup> However, these studies were of small sample size and patients were only receiving IFX induction therapy. We showed that the cumulative probability of fistula closure was 73% at 5 years and 88% at 10 years. Interestingly, after a median follow-up of 5 years, 72 (46%) of the 156 patients had sustained fistula closure. These findings underscore the beneficial effect of IFX in these patients in the long term.

Predictors of long-term outcomes in patients treated with infliximab for perianal fistulizing Crohn's disease had never been formally investigated. As observed in the population-based study from Stockholm county conducted in the pre-biologic era, we found that ileocolonic disease was

associated with a better outcome.<sup>9</sup> Available data were conflicting in PCD concerning the efficacy of concomitant immunosuppressant use. Subgroup analysis of the ACCENT II trial found that concomitant immunosuppressants did not improve response rates to IFX at one year.<sup>27</sup> By contrast, the recent SONIC trial has clearly shown therapeutic gain when IFX therapy is used in combination with azathioprine in luminal CD in immunosuppressants naïve patients.<sup>28</sup> About 12% of patients had perianal fistulas but no separate analysis was performed in this group to determine the relative benefits of single or dual therapy.<sup>28-30</sup> In a prospective study enrolling 18 patients treated with IFX, combination therapy was not associated with better outcomes, but this finding remains difficult to interpret due to small sample size.<sup>29</sup> Importantly, we could demonstrate that combination therapy was associated with higher fistula closure rates.

We also found that duration of seton drainage under 34 weeks was associated with better outcomes. In our study, removal of seton was performed for 95 of 97 patients after a median duration of 33 weeks. Little is known about the ideal removal time of seton after starting anti-TNF therapy; it is ranging from 3 weeks to 3 months in available reports.<sup>19,21,29,31,32</sup> Present *et al* found that closure of draining fistulae by IFX treatment was characterized by rapid onset (usually within 2 weeks) and a lasting benefit of action, with a median duration of closure of 12 weeks.<sup>12,33</sup> Our results are likely explained by the fact that a longer duration of seton drainage may be required in partial responders or non-responders to IFX. Short duration of seton drainage might reflect less severe disease (either less fistula tracks or less complex anatomy of the tracks), thus leading to a quicker removal of the setons. Moreover, except fistulotomy restricted to low and simple fistula, none of additional surgical procedure, including plug, fibrin glue or advancement flap was associated to clinical remission underlying the low efficacy of associated surgery for the treatment of PCD.

Recurrence of PCD after initial fistula closure was high in our study, occurring in about one third of patients during follow-up. In the ACCENT II trial, 42% of randomized patients treated with IFX as maintenance therapy experienced loss of response, including 16% of patients with recrudescence of fistulas. A prospective trial reported a 16% rate of loss of response at 18 months after IFX induction therapy followed by methotrexate maintenance therapy.<sup>21</sup> In the pre-biologic era nearly half of patients experienced fistula recurrence after first treatment of perianal fistula with only anal surgery.<sup>9</sup> Regarding perianal abscess, the ACCENT II trial showed that maintenance IFX did not result in increased abscess development in fistulizing CD (12% in the IFX group versus 17% in the placebo group).<sup>12</sup> Our data are consistent with these results as 26 patients (16.6%) developed an anal abscess after IFX therapy initiation. We found that long-term IFX treatment was associated with less abscess recurrence, further highlighting the long-term efficacy of IFX treatment in PCD.

A limitation of our study, in addition to its retrospective study design, is the absence of MRI data, as it was not routinely performed during study period. The main strengths are the duration of follow-up (about 5 years), the management of patients by experienced proctologists with a standardized monitoring on the largest cohort specifically investigating the long-term outcome of perianal fistulizing CD treated with IFX.

In conclusion, our results indicate that about two thirds of patients experienced fistula closure and one third of patients had fistula recurrence after infliximab initiation. At last follow-up, 46% of patients had sustained fistula closure. Combination therapy, duration of seton drainage < 34 weeks and long-term infliximab treatment were associated with better outcomes.

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Table 1: Baseline characteristics

Variable	Patients (n=156)
Gender (M:F)	61: 95
Median age at first IFX infusion– years (min-max)	30 (13-84)
Median disease duration – years (min-max)	3.8 (0-30)
<b>Montreal classification at first infliximab infusion – n (%; 95% CI)</b>	
Disease location	
L1 – ileal	19 (12.2 ; 7.9-18.3)
L2 – colonic	63 (40 ; 33-48)
L3 – ileo-colonic	70 (45 ; 37-53)
L4 – upper digestive tract	8 (5.8 ; 31-10.6)
Disease behavior	
B1 – non-penetrating non-stricturing	113 (72.5 ;64.9-78.8)
B2 – stricturing	19 (12.1 ; 7.9-18.2)
B3 – penetrating	24 (15.4 ;10.5-21.8)
<b>Prior treatment – n (%; 95% CI)</b>	
Purine analog (Azathioprine/6-mercaptopurine)	51 (32.7 ; 25.8-40.4)
Methotrexate	6 (3.8 ; 1.8-8.1)
Adalimumab	3 (2 ; 0.6-5.5)
Major abdominal surgery	44 (28 ; 21.7-35.7)
<b>Infliximab treatment</b>	
Regiment – n (%; 95% CI)	
Episodic	57 (36 ; 29.4-44,3)
Episodic then scheduled	9 (5,7 ; 3-10,6)
Scheduled	90 (57,7 ; 49.8-65,2)
Median duration of seton drainage before IFX – weeks (IQR75)	4 (0.6-18.1)
<b>Concomitant medications – n (%; 95% CI)</b>	
Steroids	45 (28.8 ; 22.3-36.4)
Purine analog (azathioprine/6-mercaptopurine)	82 (82.5 ; 44.7-60.2)
Methotrexate	8 (5.1 ; 23.6-9.7)
Antibiotics	90 (57.7 ; 49.8-65.2)
<b>Perianal disease – n (%; 95% CI)</b>	
Perianal Fistula according to the AGA classification	
Simple	28 (17.9 ; 12.7-24.7)
Complex	128 (82 ; 75.28-87.3)
Associated abscess	90 (58.1 ; 50.2-65.5)
Placement of seton	98 (63.22 ; 55.4-70.4)

IFX, Infliximab; CI, confidence interval; M, male; F, female

Table 2: Factors associated with first perianal fistula closure, as determined by multivariate analysis

<b>Covariates</b>	<b>HR</b>	<b>95% CI of HR</b>	<b>p-Value</b>
L1 (isolated ileal disease) behavior	0.77	0.25-1.98	0.631
<b>L3 (ileocolonic disease) behavior</b>	<b>1.88</b>	<b>1.08-3.32</b>	<b>0.0255</b>
<b>Seton drain duration &lt; 34 weeks</b>	<b>2.31</b>	<b>1.32-4.1</b>	<b>0.003</b>
<b>IFX duration &gt; 118 weeks</b>	<b>1.76</b>	<b>1.003-2.95</b>	<b>0.0485</b>
Combination therapy immunosuppressant/IFX	1.44	0.79-2.66	0.23
<b>Combination therapy immunosuppressant/IFX for naïve patients</b>	<b>2.58</b>	<b>1.16-5.6</b>	<b>0.02</b>
Simple vs Complex perianal fistula*	2.26	0.86-5.18	0.09
Interval between seton drainage and IFX initiation less than 6 weeks	1.07	0.57-2.07	0.82

HR, Hazard Ratio; IFX, infliximab;\*according to the AGA classification<sup>26</sup>;CI, confidence interval; M, male; F, female

## **Figure legends**

**Figure 1:** Flow chart of the 156 patients.

**Figure 2:** Cumulative probability of first fistula closure

**Figure 3:** Kaplan-Meier analysis of first fistula closure after infliximab therapy initiation according to predictors identified by multivariate analysis (A) Ileocolonic disease (L3) (B) Seton drainage duration (C) Long-term treatment with infliximab over 118 months (D) Combination therapy for immunosuppressants naïve patients.

**Figure 4:** Cumulative probability of fistula recurrence among the 108 patients who experienced fistula closure.

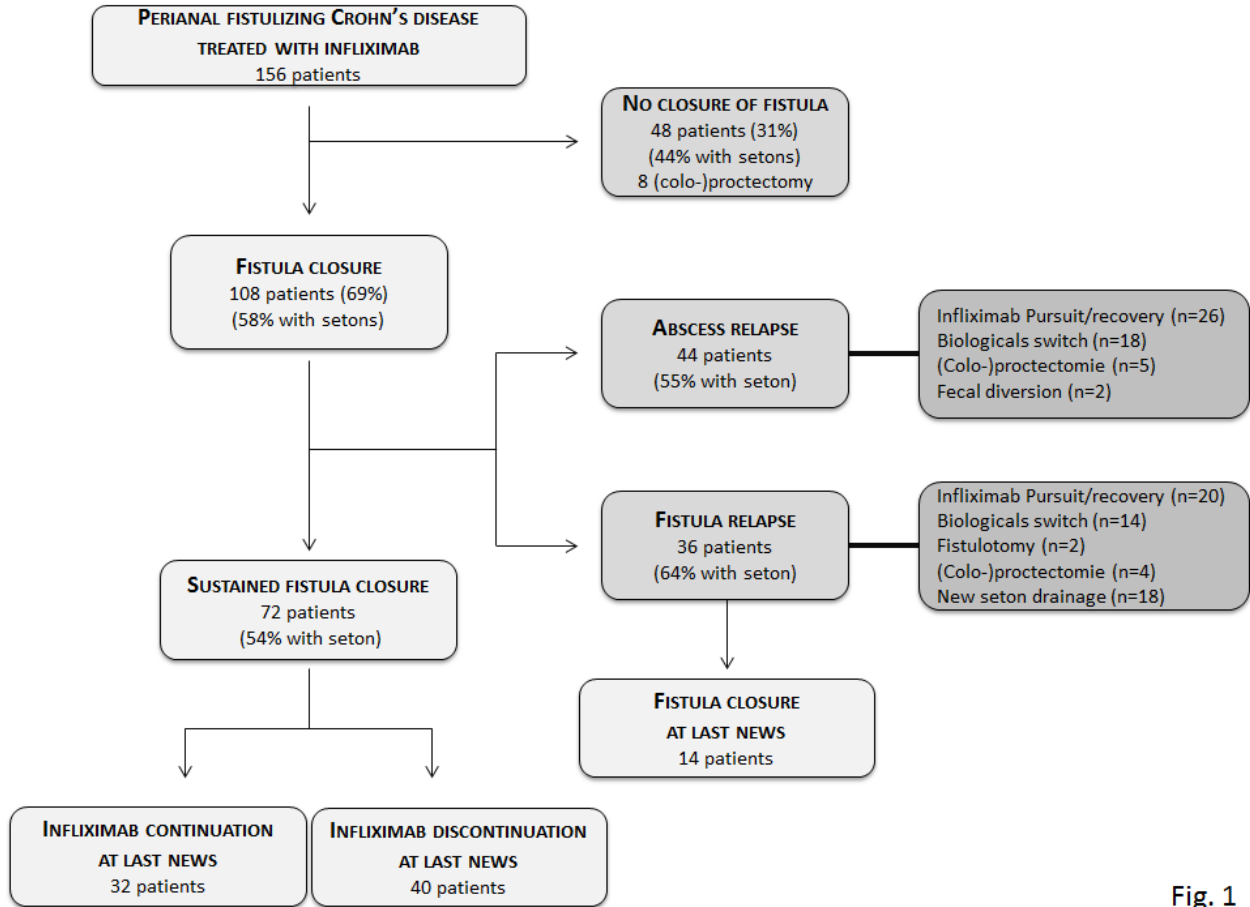


Fig. 1

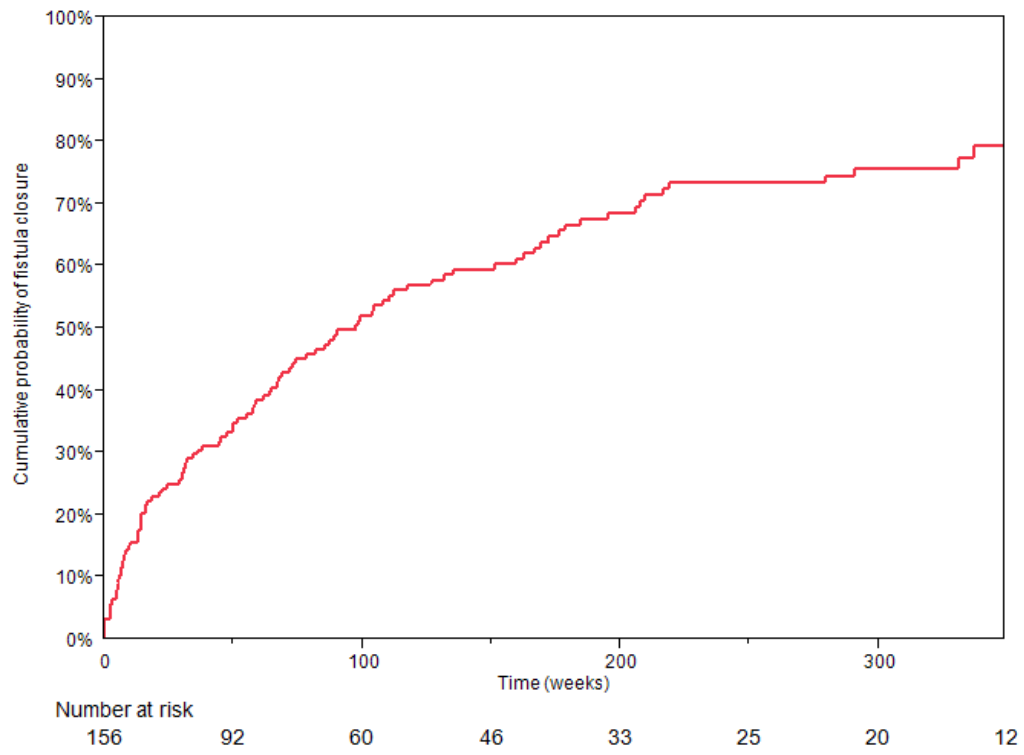


Fig. 2



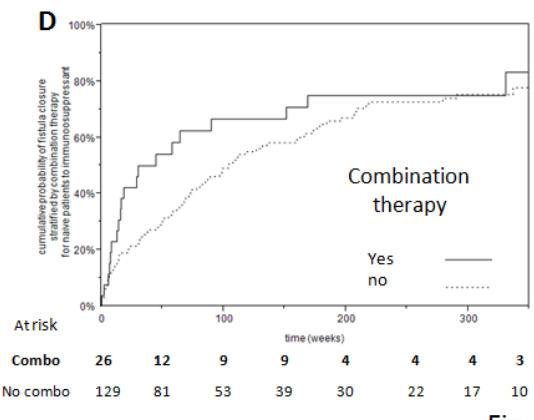
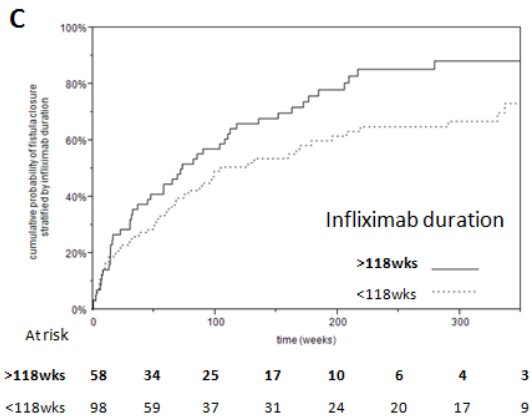
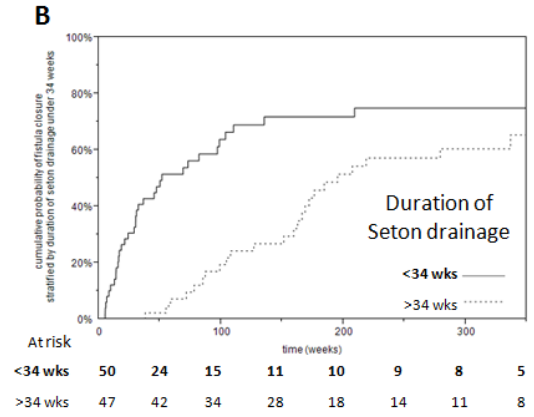
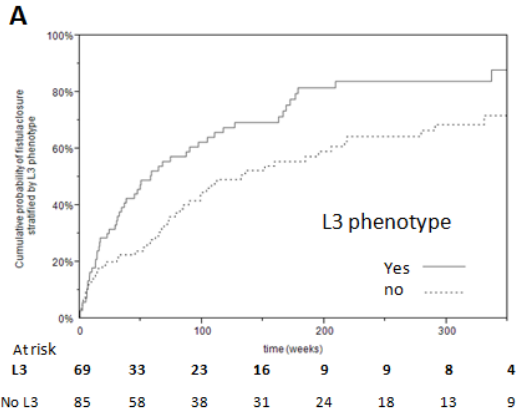


Fig. 3

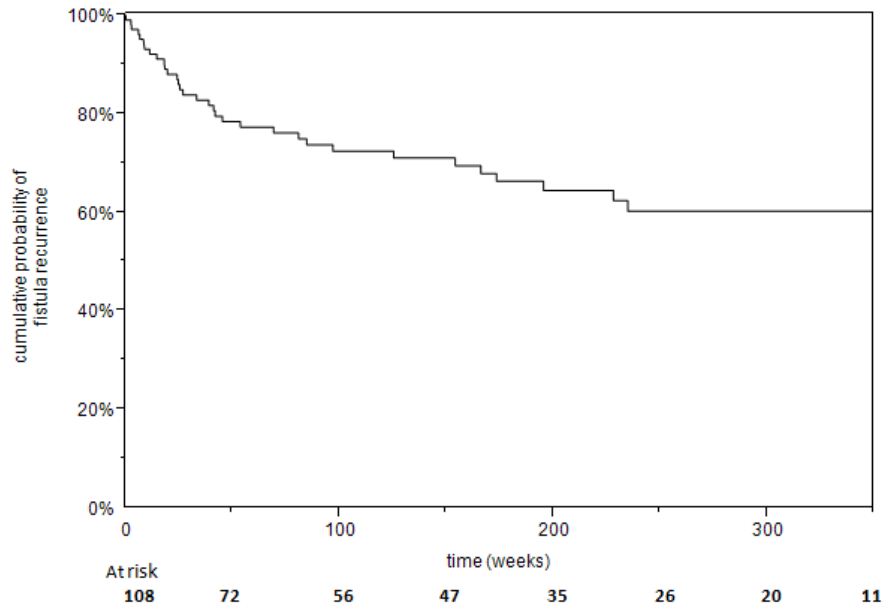


Fig. 4