

Predictors of response to infliximab in paediatric perianal Crohn's disease

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¹A list of investigators and study centres appears in the Appendix

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SUMMARY

Background

It is reported that 27–54% of paediatric patients with perianal Crohn's disease (CD) do not respond to infliximab (IFX).

Aim

To identify predictors of response to IFX in paediatric perianal CD.

Methods

A retrospective cohort study of 101 paediatric patients treated with IFX between 2000 and 2011 for perianal CD in 22 French hospitals of the GETAID pédiatrique network was performed. Response was monitored after induction therapy and at 1 year. Complete response was defined by closure of all fistulas and complete healing of ulcers. Associations between baseline characteristics and (i) 1-year response and (ii) time of first relapse among initial responders were tested by logistic regression and Cox model respectively.

Results

Eighty-nine patients (88%) responded to induction therapy (36 partial/53 complete). At 1 year, 76 patients (75%) were responders (22 partial/54 complete). Predictors of 1-year response were: number of fistulas ≤ 1 (OR: 3.76, 95% CI: 1.20–11.77, $P = 0.03$) and baseline Harvey–Bradshaw index < 5 (OR: 3.72, 95% CI: 1.10–12.60, $P = 0.03$). Predictors of relapse among initial responders were: CD duration < 10 months (OR: 3.31, 95% CI: 1.34–8.19, $P = 0.0097$) and number of fistulas > 1 (OR: 2.79, 95% CI: 1.12–6.95, $P = 0.028$). Combined therapy with an immunomodulator was not associated with 1-year response or time of relapse.

Conclusion

Those patients with perianal Crohn's disease have better outcomes if they have less fistulas, a low baseline Harvey–Bradshaw Index or a longer duration of Crohn's disease.

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INTRODUCTION

Perianal lesions are a common complication of paediatric Crohn's disease (CD), with an incidence varying from 10% to 62%.^{1, 2} Treatment of perianal lesions has long been dismaying, with high rates of recurrence and proctectomy in adult population-based studies before the era of biologic therapies.³ Infliximab (IFX) was the first anti-TNF agent to show efficacy in fistula closure.^{4, 5} Paediatric trials confirmed efficacy and safety in children with perianal lesions.^{6–9} In adults, the rates of partial and complete response at 14 weeks and 54 weeks of maintenance therapy were of 64%, 48%, 46% and 36% respectively.⁵ Higher rates of fistula closure have been observed in children. In a subgroup of paediatric patients with perianal CD from the REACH study, the rates of partial and complete response at 10 and 54 weeks of maintenance therapy were 73% and 64%, and 73% and 68% respectively.⁹ In all, at least one-fourth of patients with perianal lesions remain nonresponders to IFX. IFX being a costly drug with potentially severe adverse effects, it is paramount to identify baseline clinical predictors of response. Several studies in adults failed to identify such factors.^{10–12} However, children and adolescents have a different course of disease from adults,¹³ and may respond differently to treatment. In the present study, we aimed to identify predictors of response to IFX among paediatric patients with perianal CD. Our first objective was to identify the predictors of perianal lesions' healing at 1 year after initiation of IFX treatment. The second objective was to identify predictors of loss of response in patients who initially did respond to IFX induction therapy.

PATIENTS AND METHODS

Patients

A multicentre retrospective cohort study was conducted in 22 French paediatric gastroenterology centres, members of the Groupe d'Études Thérapeutiques des Affections Inflammatoires du tube Digestif Pédiatrique (GETAID pédiatrique). Eligible patients were 6–18 years of age, had a diagnosis of CD confirmed by endoscopy and biopsies and had perianal lesions for which a treatment with IFX had been initiated between January 2000 and December 2011. Perianal lesions were classified according to a simplified Cardiff's classification as fistulas/abscesses and/or cavitating ulcers.¹⁴ Fistulas were classified according to the criteria of Parks *et al.* as superficial, intersphincteric, transsphincteric, suprasphincteric and extrasphincteric.¹⁵ Complex fistulas were defined according to the American

Gastroenterological Association's definition as fistulas that have a high origin, may have multiple external openings, may be associated with a perianal abscess, may be associated with a rectovaginal fistula, may be associated with an anorectal stricture.¹⁶

Patients received a three-dose induction therapy at weeks 0, 2 and 6 with IFX (5 mg/kg/infusion). They were then followed 1 year after the first infusion, whether or not IFX maintenance therapy had been decided. Doses and intervals between infusions during maintenance therapy were adapted to the needs of each patient by the treating physician. Decision to do surgical drainage before IFX was also physician-driven.

Patients who had previously received IFX for luminal disease, or patients who only had anal skin lesions (Crohn skin tags) with superficial fissures were not included in this study.

Medical data were collected by the treating physicians between January 2012 and January 2013 and centralised in an anonymous database. Collected data included: sex, age at diagnosis, presence of a concomitant luminal disease, diagnostic modalities and description of perianal lesions, surgical treatment of perianal lesions before IFX, doses and intervals between infusions and concomitant treatments. Data on weight and height during follow-up were also collected. If IFX was discontinued before one full year of treatment, the reasons for discontinuation were noted.

Outcome measures

The primary endpoint was response to IFX at 1 year after first infusion. For this retrospective study, response was derived from the medical chart at the visit closest to this endpoint. Perianal disease activity was scored using the 'Fistula drainage assessment'¹⁷: 'Complete response' was defined clinically by a complete closure of all fistulas and healing of all ulcers if applicable, and 'Partial response' was defined as a reduction of 50% or more from baseline in the number of draining fistulas and/or partial healing of ulcers. Treatment was considered to have failed in the other cases or if the patient discontinued IFX before one full year of treatment due to adverse events or lack of efficacy.

Secondary analyses of efficacy evaluated the duration of response in patients who were complete or partial responders after the 3-dose IFX induction therapy. Initial response to treatment was recorded at the visit closest to 14 weeks after first infusion of IFX. Partial and complete responses were defined according to the same criterion used to define 1-year response. Patients were considered

primary nonresponders if the lesions were identical to or worse than baseline. Among initial responders, relapse was defined as a reopening of fistulas or ulcers or the formation of a new abscess during the year of follow-up. The date of relapse was the first medical visit noting a recurrence of perianal lesions.

Recaptured response, that is, a secondary closure of fistulas and ulcers, was obtained in some of the patients who relapsed, and was taken into account for the analysis of 1-year response.

Harvey–Bradshaw index (HBI) was monitored as a proxy for luminal disease activity, at initiation of IFX, after induction, and at 6 and 12 months.¹⁸ Patients with an HBI <5 were considered to be in clinical remission of their luminal disease.

Statistical analyses

The groups of responders and nonresponders were compared using *t*-tests for continuously distributed variables and Pearson's χ^2 -test or Fisher's exact tests for categorical variables. To take into account a possible 'Centre-effect' we tested for a statistical association between '1-year response' and the study centre considered as a categorical variable, using the Cochran–Mantel–Haenszel test, but none was found ($P = 0.32$). Variables associated with response to IFX in univariate analyses with a P -value <0.15 were included in a multiple logistic regression model using a stepwise selection. There were no interactions between variables. Goodness of fit of the model was assessed using a Hosmer and Lemeshow test.

To modelize duration of response, we built a survival model where an 'event' was defined by the first recurrence of perianal lesions and the 'study period' was fixed to 1 year after first IFX infusion. Patients were censored at 1 year of follow-up if no relapse was noted. They were otherwise censored if they discontinued IFX maintenance therapy before one full year because of adverse events or relapse of luminal disease without relapse of perianal disease. We selected candidate variables for the model using Log-rank tests. Quantitative variables were dichotomised using the median value of the variable as a cut-off, except for age that was divided into tertiles. Variables meeting a significance level of <0.10 were included in a Cox proportional hazards regression model, using a stepwise selection. The proportional hazards assumption was verified for all variables. Contrarily to the logistic regression model, there was a statistically significant association between study centres and the probability of loss of

response during the first year ($P < 0.0001$). We took into account this 'centre-effect' by using an analysis of clustered data in the final model, according to the method of Lee, Wei and Amato.¹⁹

P -values of less than 0.05 were considered significant. Statistical analyses were performed using SAS software, version 9.2 (Cary, NC, USA).

Ethics

The protocol was approved by the institutional review board and ethics committee (Comité de Protection des Personnes Nord Ouest III, France).

RESULTS

Patients

A retrospective chart review identified 112 paediatric patients with perianal CD who had received at least three infusions of IFX between November 2000 and December 2011. Among these, 11 patients were not included: eight had only superficial fissures and skin tags and three had previously received IFX for luminal inflammation (Figure 1).

Among the 101 included patients there were 63 males (Table 1). Mean age at diagnosis of CD was 11.5 ± 3.2 years. Mean duration of CD at initiation of IFX was 16.1 ± 17.1 months. Perianal lesions appeared before or within 1 month of diagnosis of CD in 54 patients. Perianal lesions preceded diagnosis of CD in 26 patients, by a mean 3.0 ± 4.0 months.

Diagnosis of perianal lesions was made by examination under general anaesthesia in 56 patients (55%), MRI of the pelvis in 53 patients (52%), computed pelvic tomography in 8 patients (8%), anorectal endoscopic ultrasonography in 1 patient and ultrasonography in 1 patient. Several combinations of perianal lesions were observed (Figure 2). Among the 87 patients with perianal fistulas, fistula localisation was infrasphincteric ($n = 37$), suprasphincteric ($n = 24$) and/or transsphincteric ($n = 10$). Perianal ulcers (24 patients) were localised in the anal canal ($n = 21$), the lower rectum ($n = 6$) and/or extended to the perineum skin ($n = 14$). In addition to perianal lesions, 7 patients had a rectovaginal fistula and 2, an enterocutaneous fistula. There were no anal strictures noted. Seventy-five patients (74%) had complex fistulas according to the AGA criterion¹⁶ (Table 1).

Seventy patients (69%) had an endoscopic evaluation within 3 months of beginning IFX treatment, and rectal inflammation was present in 49/70 children.

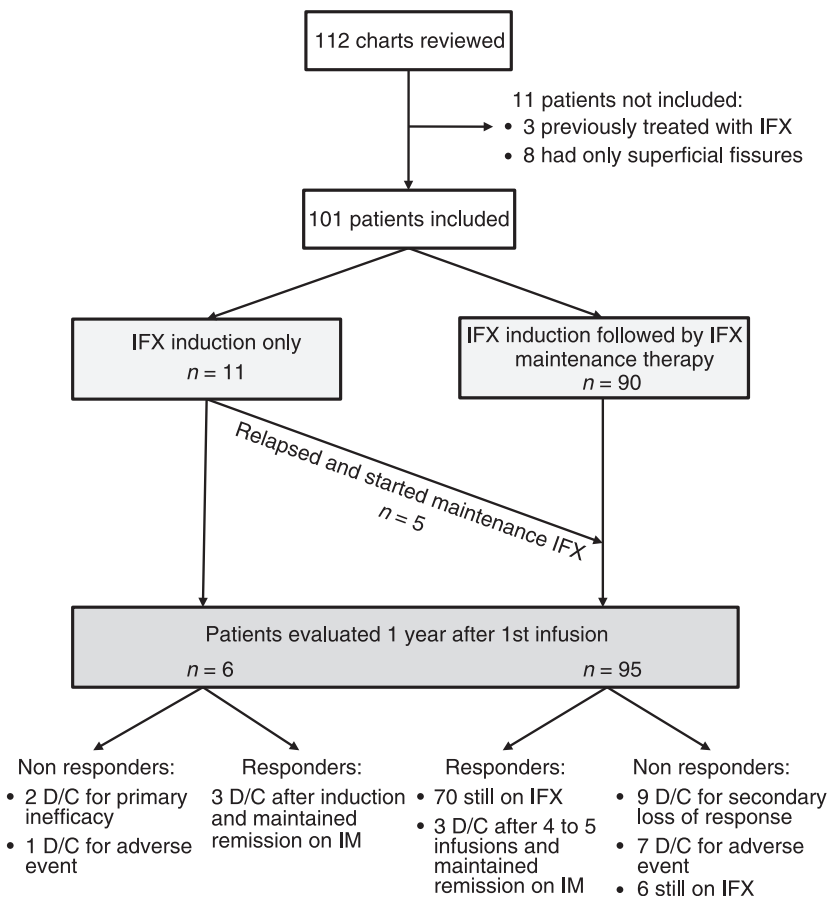


Figure 1 | Patient flow diagram. D/C, discontinued infliximab; IM, immunomodulator; IFX, infliximab.

Description of IFX treatment

Infliximab therapy was initiated at a mean 9.0 ± 13.8 months after the diagnosis of perianal lesions. Fifty-one patients received IFX for perianal lesions only, and 50 patients for perianal lesions with active luminal disease. All patients received a 3-dose induction protocol, with a median dose of IFX of 5 mg/kg per dose.

After completion of induction therapy 89 patients (88%) had responded to treatment (36 partial/53 complete) and 12 patients (12%) had not responded. In univariate analyses, 93% of patients with ≤ 1 fistula were responders after induction therapy compared to 67% of patients with >1 fistula ($P = 0.007$). The other baseline characteristics were not associated with initial response (Table 2).

After the induction protocol, maintenance IFX therapy was started in 90 patients, 8 of which had not yet experienced a response (Figure 1). IFX administration was scheduled in 81 patients (intervals between infusions <12 weeks) and episodic in 9 patients (defined as at least one interval between two infusions greater than 12 weeks). In the 'scheduled maintenance' group, mean dose of IFX during maintenance was 5.5 ± 1.1 mg/kg

per infusion (Range, 4.8–10) and mean interval between infusions was 7.3 ± 1.4 weeks (Range, 4.1–11.0). Five of the 11 patients from the 'induction only' group had a recurrence of perianal lesions during the year and IFX was resumed at a mean 20.7 ± 7.0 weeks (Range, 16.0–33.0) after the third infusion.

Dose adjustments

During the first year of IFX, treatment intensification was necessary in 42 patients (42%): an increase of at least 2.5 mg/kg/dose was necessary in 10 patients (10%), a shortening of intervals between infusions by at least two weeks was necessary in 23 patients (23%), and both these adjustments were necessary in 9 patients (9%). Dose adjustment was decided by the treating physician and could have been driven by a flare of luminal symptoms as well as to control the perianal lesions. No data on trough levels of IFX or antibodies to IFX were available.

Delayed response

Among the eight patients that were nonresponders after IFX induction but were nonetheless maintained on IFX

Table 1 | Baseline clinical characteristics of the study population. Data are expressed as Number (%) or Mean ± s.d. [Range]

Baseline characteristics	Total population (n = 101)
Sex, Male	63 (62.4)
Age at first infusion of IFX (years)	12.8 ± 3.3 [1.4–18.4]
Crohn's disease duration* (months)	16.1 ± 17.1 [0–76.0]
Perianal disease description	
Perianal disease duration* (months)	9.0 ± 13.8 [0–76.0]
Perianal disease present at onset of Crohn's disease (Yes)†	54 (53.5)
Number of fistulas	
0 fistula‡	16 (15.8)
1 fistula	67 (66.3)
>1 fistula	18 (17.8)
Complex fistulas (Yes)§	75 (74.3)
Localization of fistulas (n = 87 patients) (Several possible)	
Perianal¶	
Infrasphincteric	37
Suprasphincteric	24
Transsphincteric	10
Associated fistula, other than perianal	
Rectovaginal	7
Enterocutaneous	2
Into bladder	0
Localization of perianal ulcer (n = 24 patients) (Several possible)	
Anal canal	21
Lower rectum	6
Perineum skin	14
Rectal inflammation at baseline (Yes)**	49 (48.5%)
Previous treatments, since diagnosis of CD	
None	3 (3.0)
5 – Aminosalicylates (oral or rectal)	44 (43.6)
Antibiotics	72 (71.3)
Corticosteroids	73 (72.3)
Immunomodulators (AZA, MP, MTX)	78 (77.2)
Other biologic	1 (1.0)
Enteral nutrition	44 (43.6)
Parenteral nutrition	12 (11.9)
Previous surgery, since diagnosis of CD	
Surgical drainage	38 (37.6)
Seton	22 (21.8)
Ileocolonic resection	2 (2.0)

CD, Crohn's disease; IFX, infliximab; MP, mercaptopurine; AZA, azathioprine; MTX, methotrexate.

* Duration between date of diagnosis and date of first infusion of IFX.

† At onset: within one month of diagnosis of CD.

‡ These patients had only an abscess and/or ulcer with no evidence of perianal fistula.

§ Complex fistulas were defined according to the AGA definition as fistulas that have a high origin, may have multiple external openings, may be associated with a perianal abscess, may be associated with a rectovaginal fistula, may be associated with an anorectal stricture.

¶ Data of 21 patients were missing.

** Data of 32 patients were missing. Rectal inflammation noted on an endoscopy performed within 3 months before starting IFX.

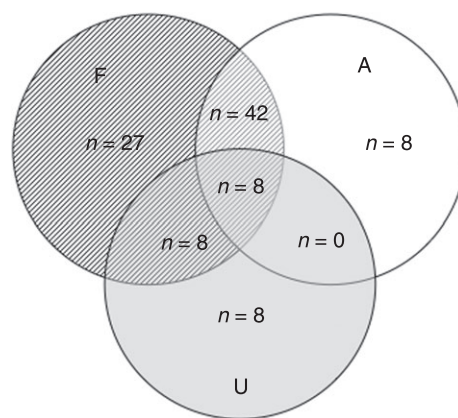


Figure 2 | Description of the types of perianal lesions observed in the 101 paediatric patients with perianal Crohn's disease, according to a simplified Cardiff's classification. Several patients had a combination of fistula (F) and/or abscess (A) and/or cavitating ulcer (U). For example, 8 patients had both at least one fistula and at least one cavitating ulcer.

therapy, four were responders at 1 year (chance of response of 50%). Among the five patients that were nonresponders at 6 months of scheduled maintenance IFX, two were responders at 1 year (chance of response of 40%).

Treatments received during the year of IFX

Seventy-four per cent of the patients were receiving combined therapy with an immunomodulator [azathioprine (n = 66) or methotrexate (n = 9)] at first infusion of IFX, 67% at initiation of maintenance therapy, 53% at 6 months and 48% at 1 year of treatment. Two naïve patients were started on an immunomodulator at initiation of IFX, and six during the year of follow-up. Seventy-two per cent of patients were receiving corticosteroids at first infusion of IFX, 15% at initiation of maintenance therapy, 4% at 6 months and 4% at 1 year of treatment.

Eight patients required surgical drainage of a perianal abscess during induction therapy with IFX (3 of which had setons inserted). Fourteen patients had at least one surgical procedure during IFX maintenance therapy: in all there were 14 abscess drainages (7 with seton insertion), 3 colostomies and 1 anal fissurectomy.

Treatment of complex fistulas

Among the 75 patients with complex fistulas, 11 (14.7%) patients had surgical drainage within the month before starting IFX and 7 (9.7%) during IFX induction. Fif-

Table 2 | Comparison of baseline characteristics of initial responders (complete or partial) and nonresponders to infliximab and one-year responders (complete or partial) and nonresponders to infliximab

Variable	Initial response (after IFX induction)			One-year response		
	Responders (n = 89)	Nonresponders (n = 12)	P	Responders (n = 76)	Nonresponders (n = 25)	P
<i>Clinical and endoscopic characteristics</i>						
Sex, Male	55 (61.8)	8 (66.7)	1	49 (64.5)	14 (56.0)	0.45
Year of initiation of IFX						
2000–2005	17 (19.1)	1 (8.3)	0.69	13 (17.1)	5 (20.0)	0.77
2006–2011	72 (80.9)	11 (91.7)		63 (82.9)	20 (80.0)	
Age at first infusion of IFX (years)	13.1 ± 2.9	10.8 ± 5.1	0.14	13.0 ± 3.0	12.3 ± 4.2	0.44
Crohn's disease duration (months)*	16.7 ± 17.8	11.3 ± 9.6	0.13	15.7 ± 16.6	17.4 ± 19.0	0.67
<i>Harvey–Bradshaw activity index</i> †						
HBI <5	29 (32.6)	4 (33.3)	1	29 (38.2)	4 (16.0)	0.07
HBI ≥5	57 (64.0)	8 (66.7)		45 (59.2)	20 (80.0)	
Rectal inflammation (Yes)‡	42 (47.2)	7 (58.3)	0.12	33 (43.4)	16 (64.0)	0.19
Granulomas present (Yes)	67 (75.3)	10 (83.3)	1	56 (73.7)	21 (84.0)	0.56
<i>Perianal disease description</i>						
Perianal disease duration (months)*	9.1 ± 14.3	8.3 ± 9.8	0.84	8.9 ± 13.2	9.6 ± 16.1	0.84
Perianal disease present at onset of CD (Yes)§	47 (52.8)	7 (58.3)	0.72	42 (55.3)	12 (48.0)	0.53
<i>Number of fistulas</i>						
0 fistula	14 (15.7)	2 (16.7)	0.007	13 (17.1)	3 (12.0)	0.12
1 fistula	63 (70.8)	4 (33.3)		53 (69.7)	14 (56.0)	
>1 fistula	12 (13.5)	6 (50.0)		10 (13.2)	8 (32.0)	
Complex fistula	66 (74.2)	9 (75.0)	0.35	59 (77.6)	16 (64.0)	0.38
Associated cavitating ulcer (Yes)	21 (23.6)	3 (25.0)	1	17 (22.4)	7 (28.0)	0.57
<i>Concomitant medication (at 1st infusion of IFX)</i>						
5 – Aminosalicylates (oral or rectal)	17 (19.1)	1 (8.3)	0.76	16 (21.1)	2 (8.0)	0.40
Antibiotics before starting IFX	62 (69.7)	10 (83.3)	0.67	53 (69.7)	19 (76.0)	0.75
Antibiotics ongoing at 1st infusion of IFX	39 (43.8)	6 (50.0)	1	36 (47.4)	9 (36.0)	0.64
Corticosteroids	38 (42.7)	5 (41.7)	1	34 (44.7)	9 (36.0)	0.79
AZA/MP	59 (66.3)	7 (58.3)	0.75	47 (61.8)	19 (76.0)	0.20
Methotrexate	6 (6.7)	3 (25.0)	0.07	6 (7.9)	3 (12.0)	0.69
Enteral nutrition (including oral Modulen®)	20 (22.5)	1 (8.3)	0.53	17 (22.4)	4 (16.0)	0.78
Parenteral nutrition	3 (3.4)	2 (16.7)	0.16	2 (2.6)	3 (12.0)	0.19
No concomitant treatment	8 (9.0)	1 (8.3)	1	7 (9.2)	2 (8.0)	0.33
<i>Surgery before IFX induction</i>						
Surgical drainage within 1 month of starting IFX¶	15 (16.9)	1 (8.3)	0.69	12 (15.8)	4 (16.0)	1
<i>Description of IFX treatment</i>						
<i>IFX treatment regimen**</i>						
Scheduled maintenance	–	–		63 (82.9)	18 (72.0)	0.43
Episodic-maintenance	–	–		6 (7.9)	3 (12.0)	
Induction only	–	–		7 (9.2)	4 (16.0)	
IM continued during the whole year of IFX	–	–		27 (35.5)	9 (36.0)	0.97

IFX, infliximab; AZA, azathioprine; MP, mercaptopurine; CD, Crohn's disease; IM, immunomodulator.

Univariate analyses using *t*-tests, χ^2 -tests or Fisher's exact tests when applicable. Data are expressed as Mean ± s.d. or *n* (%).

* Duration between diagnosis and initiation of IFX

† Data of 3 patients were missing.

‡ Colonoscopy within 3 months before initiation of IFX. Data of 32 patients were missing.

§ Perianal lesions diagnosed within one month of diagnosis of CD

¶ In 10 patients/16, drainage was combined with insertion of a seton

** 'Scheduled' defined as all intervals between infusions during the maintenance treatment <12 weeks. 'Episodic' defined as any interval ≥12 weeks. Patients in the 'Induction only' group had received three infusions and were followed up for one year. Some of the patients in the 'Induction only' group relapsed and resumed IFX during the year (See text for details).

The bold values are the *P*-values that either:

- reached significance (<0.05) in univariate analysis of initial response (Table 2)
- were <0.15 and variable was entered in the multivariable logistic regression (Table 2)
- were >0.10 and variable was entered in the cox model (Table 4).

ty-two patients (69.3%) had previously received antibiotics. IFX treatment was started under antibiotics in 32 (42.7%) patients. A sub-analysis of these patients showed that surgical drainage or antibiotics were not significantly associated with response to treatment after the induction protocol or at 1-year follow-up (Table S1). Similarly, surgical drainage within the month before starting IFX ($P = 0.13$) and antibiotics at baseline ($P = 0.87$) were not associated with relapse during the first year of follow-up. Older age was associated with initial response ($P = 0.046$) but not 1-year response. Rectal inflammation, among the 49 patients who had had an endoscopy within 3 months of starting IFX, was a negative predictor of initial response and 1-year response ($P = 0.028$ and 0.049 respectively).

Primary outcome: 1-year response

At 1 year of IFX treatment, 76 patients (75%) evidenced a response of their perianal disease (22 partial/54 complete) while 25 patients (25%) were nonresponders (Figure 1). Among the nonresponders, 6 were still on IFX and 19 had discontinued IFX due to adverse effects ($n = 8$) or lack of efficacy ($n = 11$).

The proportion of treatment failure at 1 year depending on IFX treatment regimen was 22% in the scheduled-maintenance group (18/81), 33% in the episodic-maintenance group (3/9) and 36% in the induction-only group (4/11).

Comparison of responders and nonresponders in univariate analysis (Table 2) showed that there was a trend to a higher proportion of patients with an HBi <5 at initiation of treatment in the responder group ($P = 0.07$) and a trend to a higher number of fistulas per patient in the nonresponder group ($P = 0.12$). There was no association between 1-year response and: sex, age, duration of CD, year of initiation of IFX, presence of perianal dis-

ease at onset of CD, type of perianal lesions, rectal inflammation at baseline, presence of granulomas, year of treatment, associated treatments or treatment regimen.

We compared initial response after induction therapy to 1-year response using McNemar paired tests. Response at 1-year was significantly associated with response after induction therapy ($P = 0.007$).

Using a multivariable logistic regression model, number of fistulas and HBi were independent predictors of perianal lesion healing at 1 year: the Odds Ratios were 3.76 (95% CI: 1.20–11.77, $P = 0.03$) for patients with a number of fistulas ≤ 1 and 3.72 (95% CI: 1.10–12.60, $P = 0.03$) for patients with a baseline HBi <5 (Table 3).

Secondary outcome: loss of response

Among the 89 responders after induction therapy, 27 (30%) had a relapse of perianal lesions during follow-up, with a median delay of 5.3 months (Range, 1.1–9.5), 7 patients interrupted treatment before 1 year because of adverse events or relapse of luminal disease and 55 patients reached 1 year of follow-up (Figure 3).

In univariate analyses, the variables significantly associated with relapse were CD duration <10 months ($P = 0.004$), number of fistulas >1 ($P = 0.004$) and surgical drainage within 1 month of starting IFX ($P = 0.02$) (Table 4, Figures 4–6). There was a trend to an association between relapse and concomitant aminosalicilate therapy ($P = 0.08$). Relapse was not associated with sex, age, presence of perianal lesions at onset of CD, type of perianal lesions, HBi, year of treatment or concomitant treatments (Table 4).

A multivariable Cox model clustered by study centre showed Odds Ratio of relapse of 2.79 (95% CI: 1.12–6.95, $P = 0.028$) for patients with more than one fistula, 3.31 (95% CI: 1.34–8.19, $P = 0.0097$) for patients with a

Table 3 | Predictors of response to infliximab at one year after first infusion: multivariable logistic regression

Baseline characteristic	Levels of the variable	1st model: comparison of Responders (Complete or Partial) vs. Nonresponders		2nd model: comparison of Complete responders vs. Partial responders or Nonresponders	
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
No. of fistulas	≤ 1	3.76 (1.20–11.77)	0.03	4.47 (1.36–14.71)	0.02
	>1	1		1	
HBi	<5	3.72 (1.10–12.60)	0.03	3.34 (1.30–8.62)	0.01
	≥ 5	1		1	

HBi, Harvey–Bradshaw index.

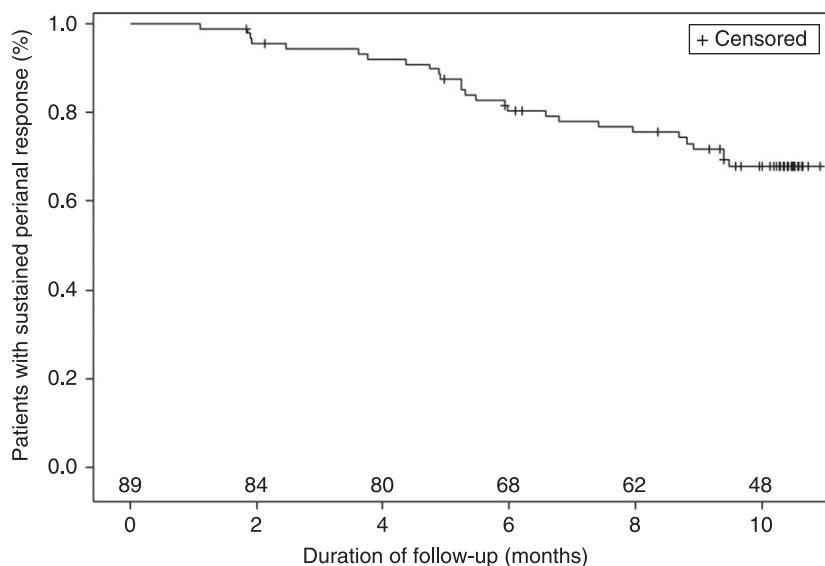


Figure 3 | Kaplan–Meier analysis of time to first loss of response to infliximab among the 89 initial responders. Loss of response was defined as reopening of perianal lesions. (Number at risk are indicated).

CD duration of less than 10 months at initiation of IFX and 2.79 (95% CI: 1.05–7.42, $P = 0.04$) for patients who had surgical drainage of their perianal lesions within 1 month of starting IFX (Table 4).

Effects on linear growth and weight

During the year of IFX treatment, the mean Z-score of Height for Age increased from -0.5 ± 1.9 at baseline to -0.3 ± 1.8 at 1 year (Table S2). The mean z-score of Weight for Age increased from -1.0 ± 1.5 at baseline to -0.5 ± 1.5 at 1 year. The mean z-score of BMI for Age increased from -1.0 ± 1.4 at baseline to -0.3 ± 1.2 at 1 year. Using a generalised linear model for repeated analysis of variance, the z-score of Weight for Age increased significantly over time within subjects ($P < 0.0001$), but there was no significant difference between responders and nonresponders. The increase of the Z-score of Height for Age did not reach significance between nor within subjects and was not associated with response.

Safety

Twenty-eight patients (28%) experienced at least one adverse event during the year of IFX treatment. Infections included gram negative septicaemia in a patient with a central venous catheter, osteitis of the sacrum ($n = 1$), varicella-zona virus infection ($n = 5$), both viral hepatitis B and zona ($n = 1$), labial herpes ($n = 1$), perianal streptococcal/staphylococcal dermatitis ($n = 1$), molluscum contagiosum ($n = 1$) and repeated viral diarrhoeas ($n = 1$). No cases of active tuberculosis were observed. Concomitant steroid therapy at baseline, con-

tinued use of immunomodulators during IFX treatment and younger age were not associated with an increased risk of opportunistic infections. Eleven allergic reactions were noted in seven patients out of the 780 infusions of IFX received by the study population ($n = 101$), a rate of 1.4 allergies for 100 infusions. Two patients had both an allergic reaction and an opportunistic infection. The other adverse events were: psoriasis ($n = 2$), a nonspecific skin rash ($n = 1$), eczema and cheilitis ($n = 1$), delayed-type hypersensitivity ($n = 1$), alopecia and headaches ($n = 1$) and chest pain during infusion ($n = 1$). No deaths or malignancies were observed. Eight patients (8%) discontinued IFX before 1 year of treatment due to adverse events.

DISCUSSION

Treatment of perianal Crohn's disease remains challenging, even since biologics have become widely used in this indication. In this large retrospective paediatric study, response rates to IFX therapy, regardless of associated treatments, were higher than those observed in adult series: partial and complete response rates at 1 year were of 75% and 53% compared to 46% and 36% in the ACCENT II study.⁵ Tolerance of treatment was similar to previous studies in children: the proportion of patients who had adverse events leading to discontinuation in our study was similar to the REACH study, 8% vs. 10% respectively.²⁰

Contrarily to earlier studies in adults who failed to identify predictive factors of response to IFX in perianal Crohn's disease,^{10–12} our study shows that a number of fistulas of less than 2, a CD duration of more than

Table 4 | Predictors of loss of response to infliximab among initial responders: univariate analyses using Log-rank tests

Variables	Levels of each variable	Univariate analysis by Log-rank tests P-value
<i>Clinical and endoscopic characteristics</i>		
Sex	M/F	0.74
Year of initiation of IFX	2000–2005 2006–2011	0.66
Age at first infusion of IFX (years)	2.8–12.2 12.2–14.6 14.6–18.4	0.23
Crohn's disease duration (months)*	<10 ≥10	0.004
Harvey–Bradshaw activity index	<5 ≥5	0.16
Rectal inflammation†	Y/N	0.74
Granulomas present	Y/N	0.61
<i>Perianal disease description</i>		
Perianal disease duration (months)*	<3 ≥3	0.15
Perianal disease present at onset of Crohn's disease‡	Y/N	0.96
Number of fistulas	≤1 >1	0.004
Complex fistulas	Y/N	0.51
Associated cavitating ulcer	Y/N	0.85
<i>Other treatments</i>		
Surgical drainage within 1 month before starting IFX§	Y/N	0.02
Concomitant medication (at 1st injection of IFX)		
5 – Aminosalicylates (oral or rectal)	Y/N	0.08
Antibiotics	Y/N	0.75
Corticosteroids	Y/N	0.47
AZA/MP	Y/N	0.36
Methotrexate	Y/N	0.46
Enteral nutrition (including oral Modulen®)	Y/N	0.17
Parenteral nutrition	Y/N	0.92
<i>Description of IFX treatment</i>		
IFX treatment regimen¶	Scheduled Episodic Induction only	0.14
IM continued during the whole year of IFX	Y/N	0.64

M/F, male/female; Y/N, yes/no; AZA/MP, azathioprine/mercaptopurine; IM, immunomodulator; IFX, infliximab.

A multivariate Cox model showed that Crohn's disease duration <10 months (OR 3.31, 95% CI: 1.34–8.19, $P = 0.0097$), a number of fistulas >1 (OR 2.79, 95% CI: 1.12–6.95, $P = 0.028$) and surgical drainage within 1 month before starting IFX (OR 2.79, 95% CI 1.05–7.42, $P = 0.04$) were associated with loss of response to IFX during the first year of treatment. Baseline concomitant treatment with 5-ASA was not associated with loss of response in the multivariate model.

* Duration between diagnosis and initiation of IFX.

† Colonoscopy within 3 months of initiation of IFX.

‡ Perianal lesions diagnosed within one month of diagnosis of CD.

§ In 10 patients/16, drainage was combined with insertion of a seton.

¶ 'Scheduled' defined as all intervals between infusions during the maintenance treatment <12 weeks. 'Episodic' defined as any interval ≥12 weeks. Patients in the 'Induction only' group had received three infusions and were followed up for one year. Some of the patients in the 'Induction only' group relapsed and resumed IFX during the year (See text for details).

The bold values are the P -values that either:

– were <0.10 and variable was entered in the cox model (Table 4).

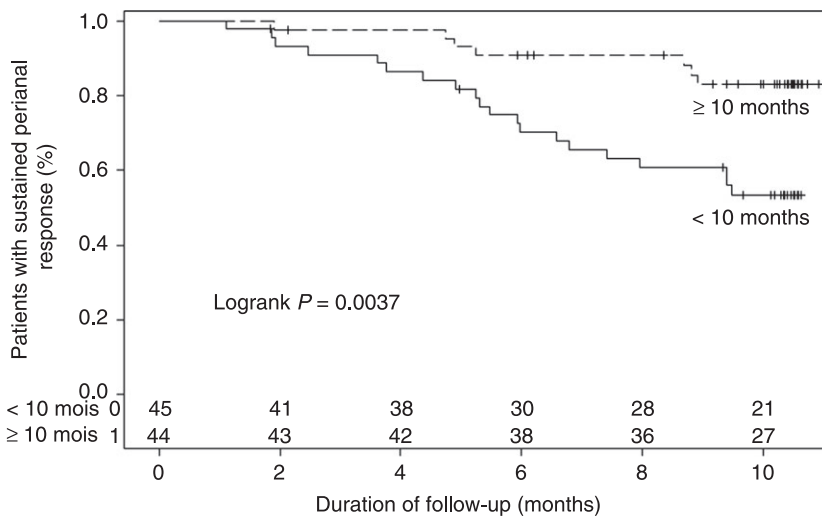


Figure 4 | Kaplan–Meier analysis of time to first loss of response to infliximab among the 89 initial responders according to duration of Crohn's disease with a cut-off of 10 months. (Number at risk are indicated).

10 months and a baseline HBi of less than 5 are associated with better outcomes. It also shows that combination therapy with an immunomodulator or surgery does not change the outcome at 1 year. Surgical drainage within the month before starting IFX was associated with loss of response during the year of follow-up.

Less fistulas and an HBi of less than 5 (a proxy for luminal disease activity) could reflect less severe phenotypes, which would be expected to respond more readily to IFX.

A shorter duration of CD (less than 10 months) at initiation of IFX increased the risk of relapse of perianal lesions by three-fold during the first year among initial responders. The presence of perianal disease at diagnosis of CD is a known predictor of disabling disease.²¹ A speculated mechanism through which these patients might relapse more than others could be a higher level of inflammation requiring higher doses of infliximab to

achieve sufficient trough levels of the drug. Trough levels of infliximab and antibodies to infliximab are increasingly used to monitor treatment and prevent loss of response.²² However, this data was not available in this retrospective study. On the other hand, 1-year response taking into account the patients that had a recaptured response during the year was not associated with duration of CD. Starting IFX early in the disease course is expected to increase the chances of a sustained response. One small retrospective study from 2003 showed that rate of response to IFX in children with perianal CD was lower in patients who had a disease duration of more than 1 year.²³ However, disparities in treatment administration and overlap between the periods before and after IFX became available prevent from any formal conclusion.

None of the concomitant treatments received at baseline was associated with 1-year response or relapse during the year of follow-up. In particular, neither baseline

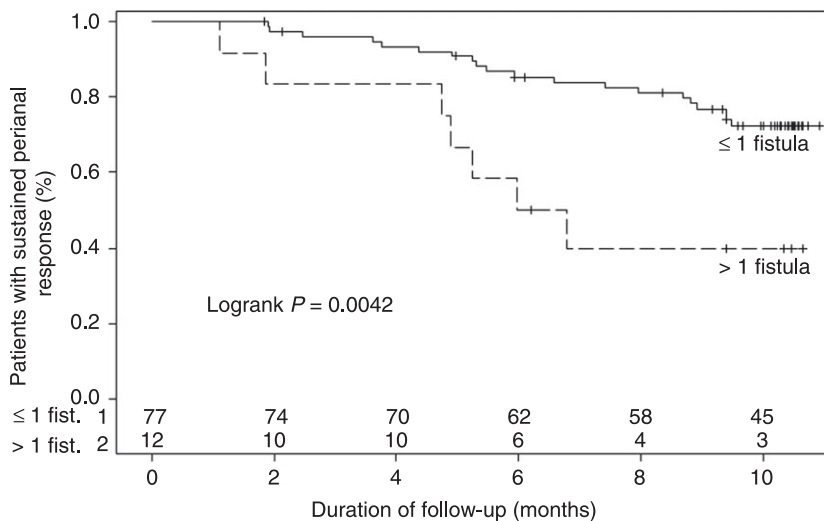
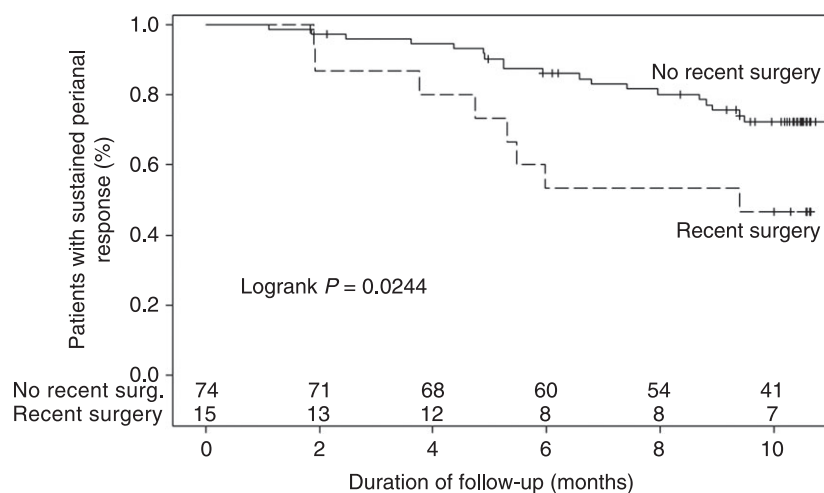


Figure 5 | Kaplan–Meier analysis of time to first loss of response to infliximab among the 89 initial responders according to the number of fistulas: 1 or less (includes patients who had an abscess or a cavitating ulcer with no evidence of a fistula) vs. more than 1 fistula. (Number at risk are indicated).

Figure 6 | Kaplan–Meier analysis of time to first loss of response to infliximab among the 89 initial responders according to recent surgical drainage: surgical drainage within one month before starting IFX vs. more than 1 month or no surgical drainage prior to IFX. (Number at risk are indicated).



treatment with immunomodulators or continued immunomodulators during the year changed the outcome of IFX. Bouguen *et al.* published two studies of predictive factors of response to IFX in adults with fistulising CD²⁴ or cavitating ulcers.²⁵ In both, combination therapy with IFX and an immunomodulator for patients naïve to immunomodulators appeared as an independent predictive factor of response. Although our rate of combination therapy was similar to theirs (75% and 83% respectively), the majority of our patients had been previously treated by immunomodulators: 77% compared to 33% in their study. The effect of combined therapy might be higher in patients naïve to both drugs. In other studies, combination therapy did not influence response or duration to response to IFX,²⁶ but was associated with higher trough levels of IFX.²⁷ Over the past ten years, reports of hepatosplenic T-cell lymphomas in young males treated with TNF- α inhibitors and thiopurines have warranted precaution.²⁸ This is a rare, but particularly severe condition, and it is important prior starting therapy to consider the benefit/risks of combination therapy.

Surgical drainage at baseline was not associated with 1-year response and did not increase initial response, even in the subgroup of patients with complex fistulas. However, the subgroup analysis might have been underpowered to show superiority of surgical drainage in combination with IFX vs. IFX alone. Considering the group of responders to induction therapy, surgical drainage prior to IFX increased the odds of relapsing during the year by 2.79. This is contradictory to previous results: small studies in adults with complex perianal fistulas showed that patients who had surgical drainage prior to IFX had a better initial response, lower rates of relapse, and a longer time to relapse than patients treated with IFX

alone.²⁹ In a randomised open-label study comparing infliximab to surgical drainage alone and to a combination of both, patients in the combination group had a shorter healing time and longer time to relapse. However, all patients with perianal sepsis underwent surgery before IFX, and patients in the surgery group but not in the IFX group received antibiotics.³⁰ As our study is retrospective, indications for and type of surgical procedures were heterogeneous. It is possible that the patients who underwent surgical drainage prior to IFX had deeper abscesses, with higher risk of recurrence. Current guidelines for management of Crohn's perianal disease state that all patients should have a surgical review at diagnosis and that abscess cavities should be evacuated. Drainage may be ensured using a silastic seton. Timing of removal of seton is not consensual.^{31, 32}

Potential limitations of the study were the number of study centres (22), a long study period with a change of prescription trends and retrospective acquisition of data. In order to limit biases, we took into account the centre effect by using a clustered analysis in the Cox model, and verified that the calendar year of IFX initiation was not associated with outcome. Methodologically, the aim of the study was to identify predictors of response to IFX, but we might have lacked power to analyse more precisely factors such as concomitant immunomodulators or prior surgical drainage and prospective randomised studies are needed. Another limitation of our study is the lack of independent evaluation of fistula status. The role of MRI is now becoming critical. Very few of the patients we studied over a ten-year period had sequential MRI exams for objective evidence of response. Future prospective studies will use MRI as an objective endpoint.³³

CONCLUSION

TNF- α inhibitors, in particular IFX, have become pivotal in the treatment of perianal Crohn's disease. This study shows that odds of response to IFX in paediatric patients with perianal CD are higher with a number of fistulas of less than 2 and a baseline HBI of less than 5. In addition, patients with a duration of CD of less than 10 months are more prone to lose response during the first year of treatment. Patients who are responders after induction therapy are more likely to be responders at 1 year of IFX.

For patients who are none responders after induction or have one or several negative predictors of response, the treating physician should consider closer monitoring of IFX therapy, an early increase in doses of IFX or changing drug classes although no study has yet shown the benefit of this strategy. Finally, the observation that combined therapy with immunomodulators does not change outcome needs further validation to tailor an optimal treatment approach for CD patients.

AUTHORSHIP

Guarantor of the article: F. Ruemmele.

Author contributions: C. Dupont-Lucas, A. Dabadie, F. Ruemmele contributed to study design, data collection,

data analysis, supervising the collection and validation of patients and manuscript preparation. C. Dupont-Lucas and C. Alberti did the statistical analyses. The other authors listed in the Appendix contributed to data collection and validation of patients and manuscript preparation. All authors approved the final version of the article including the authorship list.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of characteristics of responders and non-responders after induction and after one year of follow-up, in the subgroup of patients with complex fistulas ($n = 75$).

Table S2. Growth parameters of the study population during the first year of follow-up.

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APPENDIX 1: MEMBERS OF THE GETAID PÉDIATRIQUE AND PARTICIPATING CENTRES:

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