Predictors of Flares in Infliximab-treated Children With Inflammatory Bowel Disease

*Caroline Chabot, MD,[*] Catherine Le Berre, MD,[†,‡] Cédric Baumann, MD, PhD,[§,¶] Thomas Remen, MD,[§] Marcelo De Carvalho Bittencourt, MD, PhD,[‖,**] Silvio Danese, MD, PhD,[††,‡‡] Clémence Mercier, MD,[*] Laurent Peyrin-Biroulet, MD, PhD,[‡] and Marjorie Bonneton, MD[*]*

One third of pediatric IBD patients who initially respond to infliximab (IFX) lose that response over time. This retrospective study, including 62 children treated with IFX from 2004 to 2017, aimed to identify factors associated with clinical flare. Ulcerative colitis, extreme body mass index, and lowest IFX trough levels were associated with clinical flare in the whole population. In Crohn disease patients, perianal disease was pejorative, while location proximal to ligament of Treitz was protective. Underweight patients probably correspond to the most severe cases who are more likely to relapse, with hypoalbuminemia responsible for lower systemic IFX availability. Obesity probably induces higher IFX clearance.

Key Words: anti-TNF, flare, IBD, pediatric, therapeutic drug monitoring, weight

INTRODUCTION

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn disease (CD), might result from a complex interplay between genetic susceptibility, environmental factors, and altered gut microbiota, leading to dysregulated innate and adaptive immune responses. IBD are chronic inflammatory conditions, characterized by alternating periods of relapse and remission. The incidence of IBD in children is increasing, and pediatric clinical course is more aggressive with extensive intestinal involvement, rapid progression, and increased disease activity index compared to adult IBD.

Tumor necrosis factor (TNF)-α expression is increased in the inflamed intestinal mucosa of both adults and children with active CD.[1] Infliximab (IFX), a chimeric mouse–human monoclonal class IgG1 antibody against TNFα, inhibits the bioactivity of TNFα by directly binding to the cytokine and also modulates the function of TNFα producing cells.[2] It is current clinical practice to administer IFX via an intravenous (IV) infusion of 5 mg/kg at 0, 2, and 6 weeks for induction, followed by maintenance IV infusions every 8 weeks.

In the REACH trial, IFX induced remission in 60% of pediatric patients with CD at 1 year.[3] In a literature review, IFX has been shown to induce remission in 50%–80% of pediatric patients with IBD.[4] In addition to controlling the digestive disease, treatment with IFX allows a good recovery of growth and weight in pediatric patients.[5] The results are also satisfactory in the treatment of pediatric UC with a clinical response in 73% of children after the induction phase.[6] However, approximately one third of pediatric patients that initially respond to anti-TNF therapy will lose that response over time.[7]

Mechanisms involved in this secondary loss of response to IFX are still unclear. Low IFX trough levels (IFX TLs) have been associated with poor or partial response to IFX.[5] There are significant differences between individual IFX TLs. Young children with low body weight and those with more severe intestinal inflammation have lower levels.[6] This secondary loss of response is also related to the development of anti-IFX antibodies (IFX-Ab)[8] that appear when IFX TLs are low or even undetectable and are clearly associated with a loss of clinical

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From the *Pediatric Gastroenterology Department, Children's University Hospital of Nancy, Vandoeuvre-lès-Nancy, France; †Department of Gastroenterology, University Hospital of Nantes, Nantes, France; ‡Department of Gastroenterology, University Hospital of Nancy, Vandoeuvre-lès-Nancy, France; §Nancy University School of Medicine; INSERM, U1256, Nancy, France; ¶Platform of Clinical Research Facility PARC, Unit MDS, University Hospital of Nancy, Nancy, France; ‖Immunology Department, University Hospital of Nancy, Nancy, France; **Imopa UMR7365 CNRS/University of Lorraine, Vandoeuvre-lès-Nancy, France; ††IBD Center, Department of Gastroenterology, Humanitas Clinical and Research Centre, Milan, Italy; ‡‡Department of Biomedical Sciences, Humanitas University, Milan, Italy

Address correspondence to: Laurent Peyrin-Biroulet, Department of Gastroenterology, University Hospital of Nancy, 1 Allée du Morvan, 54 511 Vandœuvre-lès-Nancy, France (peyrinbiroulet@gmail.com).

C.C., C.L.B., and C.B. contributed equally to this work.

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response in adult patients.[9] In pediatric IBD, IFX-Ab correlate with reduction in IFX TLs and a higher risk of surgery.[10] Dose optimization and assessment of antibody formation is a current practice to address the risk of relapse with IFX use.

Other factors seem to be associated with secondary loss of response. Studies on adult IBD cohorts demonstrated that older age, high body mass index (BMI), previous surgery and colonic disease were associated with nonresponse to IFX induction therapy.[11,12] Two studies demonstrated that a C-reactive protein (CRP) value above 5 mg/L during IFX therapy might also predict a subsequent relapse.[13,14]

Conversely, a high colitis activity index before IFX therapy has been shown to be an independent positive predictor for response to IFX in UC patients.[15] Biomarkers, especially normal albumin level, might also be predictive of remission.[16]

In pediatric IBD, data on potential predictors of relapse are scarce. The main study that investigated this issue identified low BMI (BMI scores based on international expert guidelines),[17] growth failure, abnormal CRP (>5 mg/L) after induction, and failure to use concomitant immunomodulators as independent factors associated with increased loss of response to IFX maintenance therapy in CD.[18] Another CD pediatric study demonstrated that the probability of loss of response to IFX did not depend on the location nor the behavior of the disease.[19]

There are many described potentially predictive factors of relapse in children with IBD but available data refer only to CD, and there is high heterogeneity in study design and in definitions of loss of response. Thus, there is no clear guidance for the risk of relapse in IBD pediatric patients treated with IFX in current clinical practice. It is therefore important to identify predictors of response to optimize treatment and improve the benefit/risk ratio of anti-TNF use in pediatric patients.

There is no consensus on the influence of BMI, sex, age at first IFX infusion, and disease location on the response to IFX in pediatric IBD. We hypothesized that those clinical factors which vary widely in children with IBD may influence treatment response.

In this study, we aimed to identify such predictive factors of clinical flare to IFX among pediatric patients with IBD.

MATERIALS AND METHODS

Study Design

This retrospective study included all pediatric IBD patients (CD and UC) treated with IFX from January 2004 to December 2017 at the Children's University Hospital of Nancy. Patients had to be under 18 years of age at IBD diagnosis defined on the Porto criteria.[20] Age at diagnosis, age at onset of IFX therapy, location, and behavior of IBD according to Paris classification,[21] and previous or concomitant treatments were collected at baseline.

IFX was administered by IV infusions at the dose of 5 mg/kg at 0, 2, and 6 weeks (induction), followed by maintenance therapy every 8 weeks. IFX treatment could be optimized (increase in the dosage up to 10 mg/kg and/or shorten interval between infusions). Treatment intensification could be performed at the discretion of the physician.

At each infusion, a physical examination was performed by a pediatric gastroenterologist. Harvey Bradshaw Index (HBI) was calculated for CD patients, and Pediatric Ulcerative Colitis Activity Index (PUCAI) was used in UC patients. Clinical flare was defined by a score HBI ≥5 or PUCAI ≥10. BMI data were collected at each infusion.

From the fourth infusion (ie, after induction phase), biological analyses were performed before each IFX infusion for all patients, including hemoglobin, platelets, CRP, albumin, IFX TLs, and IFX-Ab. All analyses were carried out in the same laboratory of the University Hospital of Nancy. IFX TLs and IFX-Ab were quantified using specific enzyme-linked immunosorbent assay (ELISA) kits commercially available following the manufacturer's protocol (Theradiag, France).

A stool sample was also collected at each infusion, stored at room temperature and sent to the University Hospital of Lille for the measurement of fecal calprotectin (FC).

At the discretion of the physician, patients could be seen during a routine follow-up visit at 1 year after initiation of IFX therapy. For the patients who performed this visit, primary clinical remission was defined at that time by the absence of clinical flare since their inclusion.

Each included patient was followed up until December 31, 2017, or alternatively the date on which the patient was transferred to the adult gastroenterology unit or to another care location.

Statistical Analysis

For the main analyses, all visits performed from the 4th infusion were considered. Categorical variables were described using number and percentage and continuous variables, by quartiles [median (first, third quartiles)]. Because several measures were available for each patient, with a significant "patient" effect, a multilevel model was chosen, in bivariate, for the selection of variables. Variables with a P value <0.05 in bivariate analysis models were then analyzed in a multivariate one-level hierarchical linear models (HLM).[22] The same procedure was applied in each IBD subgroup (UC and CD). For the purposes of the model (respect of assumptions), age at visit, BMI and IFX trough levels were transformed into categorical variables: age in 3 modalities according to the tertiles thresholds, BMI in 3 classes divided according to the thresholds <18.5; 18.5–25; >25, and IFX TL in 5 modalities according to the quintiles thresholds obtained in the whole population: <1.0; (1.0–3.3); (3.3–6.4); (6.4–10.1); and ≥10.1; and then in each subgroup of IBD. In the CD subgroup (n = 53), the thresholds were <1.0; (1.0–3.2); (3.2–6.1); (6.1–9.5); and ≥9.5. In the UC subgroup (n = 9), only 3 classes of IFX TL have been defined (tertiles) because the number of measures was low: <2.8; (2.8–11.1); and ≥11.1.

Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) with a significance level set at 0.05.

RESULTS

Baseline Characteristics

A total of 62 patients having received IFX in our center were enrolled, with a total of 866 IFX infusions (Table 1). The median (range) ages at diagnosis of IBD and at onset of IFX therapy were 11.2 (0.6–17.5) and 13.2 (3.5–19.8) years, respectively. There were 54.8% males. Most patients had CD (n = 53, 85.5%), the location being mainly ileocolonic (L3) (n = 42, 79.2%) and/or proximal (L4) (n = 36, 67.9%). Thirty-three of patients with CD (62.3%) had a nonstricturing nonpenetrating phenotype (B1). CD was associated to perianal disease and growth retardation in 58.5% and 96.2% of cases, respectively. Nine patients (14.5%) were diagnosed with UC, including 6 patients (66.7%) with pancolitis (E4). Seven patients (77.8%) with UC never had severe disease (S0). Eighteen patients (29%) had extra-intestinal manifestations. Among these patients, 14 (77.8%) had arthralgia, 7 (38.9%) had asthenia, and 2 patients (11.1%) had aphthous ulcers.

Fifty-eight of all IBD patients (95.1%, one data missing) were receiving another treatment before initiation of IFX, including azathioprine (88.0%), corticosteroids (88.0%), methotrexate (17.2%), Modulen (58.6%), and mesalazine (27.6% oral and 5.2% topical).

At the first IFX infusion, median BMI was 16.8 kg/m^2 [14.3–19.0], median CRP was 14.3 mg/L [3.1–36.8], and median fecal calprotectin was 511.5 µg/g [264–860]. Thirty-seven patients (88.1%, one data missing) had another treatment for IBD combined with IFX therapy: azathioprine (for 64.9% of these patients), corticosteroids (43.2%), enteral nutrition (32.6%), mesalazine (4.8%), and methotrexate (4.8%).

IFX Therapy Outcomes

Fifty-four patients (87.1%) performed the follow-up visit after 1 year of IFX. Median BMI was 19.3 kg/m^2 [17.0–20.5], median CRP was 1.4 mg/L [0.8–10.7], and median FC 236 µg/g [34.0–464.0]. Among these 54 patients, 41 patients (78.8%, 2 data missing) were in primary clinical remission (ie, no flare between inclusion and follow-up visit at 1 year after initiation of IFX therapy) (Fig. 1).

The median duration was 2.5 years [0.3–7.2]), 32 patients (51.6%) had experienced one flare or more since their inclusion (Fig. 1). IFX treatment was stopped for 17 (27.4%) patients. The main reasons for stopping treatment were allergy (47.1%), inefficacy (29.4%), and infection (17.7%). Among them, 7 patients (41.2%) started adalimumab therapy.

Regarding hospitalizations, 20 patients (32.3%) were hospitalized once, 10 (16.1%) twice, and 5 (8.1%) 3 times. The main reasons for hospitalization were flare (35% for the first hospitalization) or infection (20.0%).

TABLE 1. Baseline Demographic and Clinical Characteristics

Demographic and Clinical Data	Total (n = 62)
Male sex, n (%)	34 (54.8)
Age at IBD diagnosis (y), median (range)	11.2 (0.6–17.5)
Age at first IFX infusion (y), median (range)	13.2 (3.5–19.8)
Crohn's disease, n (%)	53 (85.5)
Location	
L1, n (%)	8 (15.1)
L2, n (%)	3 (5.7)
L3, n (%)	42 (79.2)
L4, n (%)	36 (67.9)
Behavior	
B1, n (%)	33 (62.3)
B2, n (%)	11 (20.8)
B3, n (%)	14 (26.4)
B2 + B3, n (%)	0 (0.0)
Perianal, n (%)	31 (58.5)
Growth retardation, n (%)	51 (96.2)
Ulcerative colitis, n (%)	9 (14.5)
Location	
E1, n (%)	0 (0.0)
E2, n (%)	2 (22.2)
E3, n (%)	1 (11.1)
E4, n (%)	6 (66.7)
Severity	
S0, n (%)	7 (77.8)
S1, n (%)	2 (22.2)
Previous medication, n (%)	58 (95.1)
Azathioprine, n (%)	51 (88.0)
Corticosteroids, n (%)	51 (88.0)
Methotrexate, n (%)	10 (17.2)
Modulen, n (%)	34 (58.6)
Oral mesalazine, n (%)	16 (27.6)
Topical mesalazine, n (%)	3 (5.2)
Concomitant medication, n (%)	37 (88.1)
Azathioprine, n (%)	24 (64.9)
Corticosteroids, n (%)	16 (43.2)
Methotrexate, n (%)	2 (4.8)
Modulen, n (%)	14 (32.6)
Mesalazine, n (%)	2 (4.8)

IBD, inflammatory bowel disease; IFX, infliximab.

Association of IFX Trough Levels With Remission

Median IFX TL throughout the 866 IFX infusions was 4.8 µg/mL [0.0–25.0]. IFX TL were significantly lower in patients who failed IFX therapy than in those in remission (1.9 µg/mL vs 5.1 µg/mL, $P < 0.0001$), this difference being independent of the IFX dose received (0.9 µg/mL vs 4.1 µg/mL,

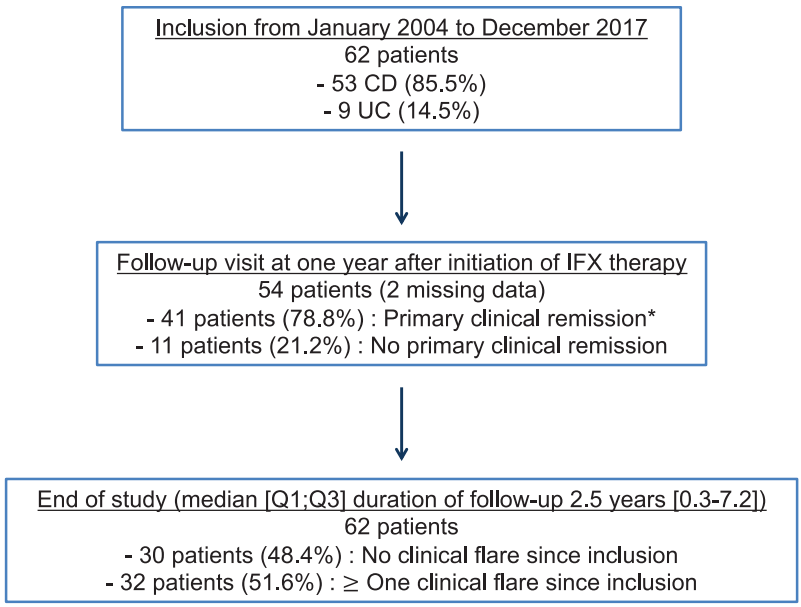

FIGURE 1. Flowchart of the study.

TABLE 2. Serum Infliximab Trough Levels (IFX TLs, µg/mL) in Pediatric IBD Patients (62 Patients)

	Total		Remission		Flare		*P**
IFX Doses/Weight	n	Median IFX TLs [Range]	n	Median IFX TLs [Range]	n	Median IFX TLs [Range]	
5 and 10 mg/kg	866	4.8 [0.0–25]	753	5.1 [0.0–25.0]	113	1.9 [0.0–17.0]	<0.0001
5 mg/kg	438	3.8 [0.0–25]	401	4.1 [0.0–25.0]	37	0.9 [0.0–13.0]	<0.0001
10 mg/kg	400	5.9 [0.0–21.1]	327	6.4 [0.0–21.1]	73	2.7 [0.0–17.0]	<0.0001

IBD, inflammatory bowel disease; IFX, infliximab; TL, trough level.
*Wilcoxon test.

$P < 0.0001$ and 2.7 µg/mL vs 6.4 µg/mL, $P < 0.0001$ for doses at 5 and 10 mg/kg, respectively) (Table 2).

There was no correlation between BMI and IFX TL (Spearman coefficient = 0.26, $P = 0.140$).

Predictors of Clinical Flare

Results of bivariate and multivariate analyses for the whole IBD population are presented in Table 3. In bivariate analysis, 4 variables were associated with clinical flare: sex, type of IBD, BMI, and IFX TL. In multivariate analysis, the type of IBD, BMI, and IFX TL were significantly associated with clinical flare. UC patients had a significantly higher probability of clinical flare than CD patients (OR = 83.0, 95% confidence interval [CI] = 8.3–833.6), as well as underweight and overweight compared with patients with normal body weight (OR = 3.4, 95% CI = 1.3–9.0 and OR = 4.6, 95% CI = 1.2–18.3, respectively). Conversely, patients with an IFX TL comprised between 6.4 and 10.1 (OR = 0.2, 95% CI = 0.0–0.5) and patients with an IFX TL higher than 10.1 (OR = 0.2, 95% CI = 0.0–0.5) had a lower probability of clinical flare than patients having an IFX TL below 1.0.

In the CD subgroup (n = 53), the bivariate analysis showed that 5 variables were significantly associated with clinical flare: BMI, IFX TL, IFX-Ab, perianal disease, and upper disease proximal to ligament of Treitz (L4a location) (Table 4). In multivariate analysis, 3 variables were still associated with clinical flare: BMI, perianal disease and L4a disease location. Underweight OR = 3.9, 95% CI = 1.2–12.7) and overweight (OR = 11.8, 95% CI = 1.9–71.5) patients had a higher probability of clinical flare than patients with normal body weight. Similarly, patients with perianal disease had a higher probability of clinical flare than patients without perianal disease (OR = 4.7, 95% CI = 1.1–20.5). Conversely, upper disease location proximal to ligament of Treitz was associated with a lower probability of clinical flare (OR = 0.1, 95% CI = 0.0–0.6). Patients with an IFX TL comprised between 6.1

TABLE 3. Predictive Factors of Clinical Flare in the Whole Population of IBD Patients (n = 62)

	Bivariate Analysis		Multivariate Analysis	
Variables	OR [95% CI]	*P*	OR [95% CI]	*P*
Sex (male vs female)	0.2 [0.0–1.0]	**0.0488**	—	—
Type of IBD (UC vs CD)	92.3 [9.0–946.7]	**0.0001**	83.0 [8.3–833.6]	**0.0002**
IFX TL				
Reference 1st quintile	1.0	**0.0050**	1.0	**0.0105**
2nd quintile vs 1st quintile	0.4 [0.1–0.9]		0.3 [0.1–0.9]	
3rd quintile vs 1st quintile	0.3 [0.1–0.8]		0.3 [0.1–0.8]	
4th quintile vs 1st quintile	0.2 [0.1–0.6]		0.2 [0.0–0.5]	
5th quintile vs 1st quintile	0.1 [0.0–0.4]		0.2 [0.0–0.5]	
IFX dose regimen (10 mg/kg vs 5 mg/kg)	1.4 [0.6–3.1]	0.4191	—	—
BMI		**0.0006**		**0.0066**
BMI <18 vs normal	5.7 [2.2–15.2]		3.4 [1.3–9.0]	
BMI >25 vs normal	3.9 [1.0–15.9]		4.6 [1.2–18.3]	
Age		0.7324		—
Age <11.5 y vs >15 y	1.3 [0.1–12.9]		—	
Age 11.5–15 y vs >15 y	0.5 [0.1–5.4]		—	

Bold values correspond to *P*-values that are statistically significant (<0.05).
BMI, body mass index; CD, Crohn disease; CI, confidence interval; IBD, inflammatory bowel disease; IFX, infliximab; OR, odds ratio; TL: trough level; UC, ulcerative colitis.

and 9.5 (OR = 0.3, 95% CI = 0.1–1.3) and those with an IFX TL higher than 9.5 (OR = 0.4, 95% CI = 0.1–1.2) tended to have a lower probability of clinical flare than patients having a IFX TL below 1.0, although it was not statistically significant (*P* = 0.0943) (Table 4).

In the UC subgroup (n = 9), 3 variables were associated with clinical flare in bivariate analysis: age, BMI, and IFX TL. Among them, only IFX TL was still associated with clinical flare in multivariate analysis. Compared to patients having an IFX TL <2.8, those with an IFX TL between 2.8 and 11.1 (OR = 0.2, 95% CI = 0.0–0.9) and those with an IFX TL >11.1 (OR = 0.0, 95% CI = 0.0–0.4) had a lower probability of having a clinical flare.

Safety Data

Immediate and delayed adverse events after IFX infusion were reported in 16 (25.8%) and 19 (30.6%) patients, respectively. Among immediate adverse events during infusion, patients mainly reported head pain (31.3%), labial or laryngeal edema (31.3%), desaturation (18.8%). One patient had an anaphylactic shock. Because of these side effects, IFX treatment was definitively stopped for 6 (37.5%) of these patients. Among delayed adverse events, 8 patients (42.1%) had paradoxical psoriasis, 4 (21.1%) had head pain, 3 (15.8%) had muscle pain, and 6 patients (31.8%) had severe infections.

DISCUSSION

This retrospective study investigated the predictors of treatment failure in 62 pediatric patients (ie, 866 infusions) diagnosed with IBD treated with IFX, and identified UC, extreme BMI (underweight and overweight), and low IFX trough levels as predictive factors of flare considering all IBD patients together. In CD patients, perianal disease was associated with clinical flare, while upper disease location proximal to ligament of Treitz was protective.

In our study, disease remained active in 51.6% of patients. Serum IFX TLs of patients with clinical remission were higher than those in patients with a poor response. Median IFX TLs were 4.8 µg/mL (5.1 µg/mL among responders vs 1.9 µg/mL among nonresponders). Recent studies have reported similar median IFX TLs.[5,11]

It is also important to note the weak proportion of patients with UC in our cohort (14.5%). Recently, Merras-Salmio and Kolho[5] published a study with 146 pediatric patients having received IFX in Finland, including 70% with CD. A Scottish multi-center group also published their anti-TNF experience in pediatric patients, with 85% CD patients out of 127 participants,[23] confirming that CD is the most prevalent type of IBD in children.

Grover et al[18] also demonstrated that loss of clinical response was associated with lower BMI in a pediatric cohort of IBD patients. Another study showed that BMI in the lower and upper quartiles was associated with more severe disease course in children with IBD.[24] Several factors may explain these results. For underweight patients, it is likely that they include the most severe cases of IBD responsible for subnutrition and therefore more likely to relapse. These patients are also likely to have a more severe hypoalbuminemia, which may be responsible for a lower systemic availability of IFX therapy and change its pharmacokinetics. In addition, it has also been suggested that

TABLE 4. Predictive Factors of Clinical Flare in the Subgroup of Patients With CD (n = 53)

	Bivariate Analysis		Multivariate Analysis	
Variables	OR [95% CI]	*P*	OR [95% CI]	*P*
Sex (male vs female)	0.2 [0.0–1.4]	0.1051	—	—
IFX TL				
Reference 1st quintile	1.0	**0.0119**	1.0	0.0943
2nd quintile vs 1st quintile	0.1 [0.0–0.5]		0.2 [0.1–0.8]	
3rd quintile vs 1st quintile	0.2 [0.0–0.6]		0.2 [0.1–1.0]	
4th quintile vs 1st quintile	0.2 [0.1–0.8]		0.3 [0.1–1.3]	
5th quintile vs 1st quintile	0.3 [0.1–0.9]		0.4 [0.1–1.2]	
IFX dose regimen (10 mg/kg vs 5 mg/kg)	1.7 [0.7–4.2]	0.2552	—	—
IFX Ab (present vs absent)	3.5 [1.3–9.1]	**0.0122**	—	—
BMI		**0.0039**		**0.0077**
BMI <18 vs normal	6.5 [1.7–25.4]		3.9 [1.2–12.7]	
BMI >25 vs normal	20.2 [1.8–221.1]		11.8 [1.9–71.5]	
Age		0.6157		—
Age <11.5 y vs >15 y	0.6 [0.1–5.5]		—	
Age 11.5–15 y vs >15 y	0.3 [0.0–3.0]		—	
Disease location				
L1 (yes vs no)	0.5 [0.0–7.0]	0.6050	—	—
L2 (yes vs no)	4.2 [0.0–404.5]	0.5343	—	—
L3 (yes vs no)	1.2 [0.1–13.3]	0.8666	—	—
L4a (yes vs no)	0.1 [0.0–0.4]	**0.0013**	0.1 [0.0–0.6]	**0.0110**
L4b (yes vs no)	0.8 [0.1–4.8]	0.7746	—	—
Disease behaviour				
B1 (yes vs no)	0.2 [0.0–1.4]	0.1167	—	—
B2 (yes vs no)	3.4 [0.3–34.5]	0.3070	—	—
B3 (yes vs no)	0.6 [0.1–4.9]	0.6732	—	—
Perianal disease (yes vs no)	6.7 [1.4–33.0]	**0.0189**	4.7 [1.1–20.5]	**0.0374**

Ab, antibody; BMI, Body mass index; CD, Crohn's disease; CI, Confidence interval; IFX, Infliximab; OR, Odds ratio; TL: Trough level.

children with lower body weight had significantly lower IFX TLs during induction therapy.[6]

Obesity is recognized as a chronic low-grade inflammatory condition. There have been several studies that identified elevated BMI and body fat as risk factors for poorer response to anti-TNFα treatment, and at equal IFX TLs, patients with a higher BMI and body fat had 20% increased likelihood of loss of response.[11] The pharmacokinetic mechanisms by which this occurs remain unclear. Dotan et al[25] confirmed these results in an adult cohort and showed that the clearance of IFX is increased in case of hypoalbuminemia and overweight. Our results suggest the same trend in children, but these results need to be confirmed in prospective studies. Indeed, the prevalence of pediatric obesity is increasing, and it will be essential to know the changes in the bioavailability of these drugs according to the weight of our patients.

In our study, perianal CD was also associated with clinical flare. Perianal lesions are a common complication of pediatric CD, with an incidence varying from 8% to 94%.[26] In our study, among 53 CD patients, 58.5% had perianal lesions. Anti-TNFα agents, especially IFX, showed efficacy in fistula closure. Pediatric trials confirmed efficacy and safety in children with perianal lesions.[27] Dupont-Lucas et al[28] showed that a number of fistulas less than 2 and a baseline HBI less than 5 might be associated with better outcomes, but this could reflect less severe disease, which would be expected to respond more readily to IFX. The presence of perianal disease at diagnosis of CD is known as a predictor of disabling disease.[29] A speculated mechanism through which these patients might relapse more than others could be a higher level of inflammation requiring higher doses of IFX to achieve sufficient TLs of the drug.

Our study has some limitations. The most important limitation was the lack of distinction between primary nonresponse and the secondary loss of response to IFX, mainly due to its retrospective design more than 13 years. Data from the infusions during which clinical activity scores were elevated, defining clinical flare, were included without taking into account

the previous infusions or the previous clinical response. Second, our sample was held in a referral center probably including more severe patients with higher rates of complications, surgery and having a higher need for anti-TNF compared with the whole IBD population in general. This sampling specificity could limit the extrapolation of our results. Finally, the low number of patients, particularly in the UC subgroup, has probably limited the ability of statistical analyses to highlight certain associations.

In conclusion, the identification of factors predictive of clinical flare in pediatric IBD patients would be of great advantage for directing treatment changes at an earlier stage to expedite clinical improvement, reduce the risk of adverse events, and improve the cost-effectiveness of IFX therapy in these patients. This study shows that therapeutic drug monitoring could be of great use in this indication, especially in patients with extreme BMI, although these findings must be confirmed by further prospective studies distinguishing primary nonresponse and secondary loss of response.

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