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Efficacy of infliximab after loss of response of/intolerance to adalimumab in pediatric Crohn's disease: A retrospective multicenter cohort study of the "GETAID pédiatrique"

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Abstract

Background: Infliximab (IFX) and adalimumab (ADA) are recommended for induction and maintenance of remission in pediatric Crohn's disease (CD). ADA is now often used in first line due to its efficacy and tolerability, but a loss of response (LOR) can occur over time. The aim was to assess the efficacy of IFX as second line therapy after LOR or intolerance to ADA in pediatric CD patients at 1 year.

Methods: We conducted a retrospective and multicenter study in France among the "GETAID pédiatrique" centers between April 2019 and April 2022. CD patients under 18 years old and treated with IFX after ADA failure or intolerance were included. We collected anthropometric, clinical, and biological data at baseline (start of IFX), at 6 and 12 months. Clinical remission was defined by a Weighted Pediatric CD Activity Index (wPCDAI) score less than 12.5 points.

Results: Of the 32 patients included in our study, 27 (84.4%) were still on IFX at 12 months of the switch. Among them, 13 had discontinued ADA because of a LOR, 12 for insufficient response and 2 due to primary nonresponse. At M12, 22 patients were in corticosteroid free clinical remission (68.7%). Under IFX, the wPCDAI decreased over time (47.5 ± 24.1, 16.6 ± 21.2 and 9.7 ± 19.0 at M0, M6 and M12 respectively). The only factor associated with clinical remission at 12 months was absence of perianal disease at the end of the IFX induction.

Conclusions: IFX is effective in maintaining remission at 1 year in pediatric CD patients experiencing a LOR or intolerance with ADA, and IFX could be an interesting therapeutic choice instead of other biologics in this situation.

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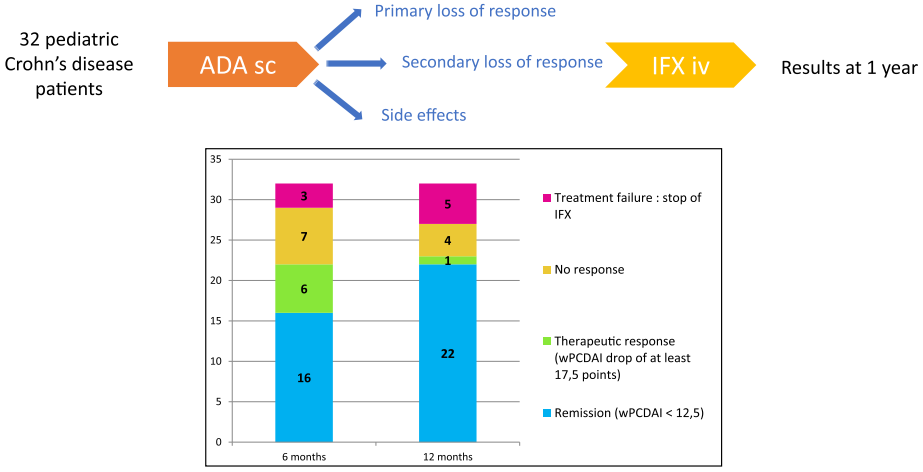

KEYWORDS
anti-TNF-α, children, switch

1 | INTRODUCTION

Antitumor necrosis factor (anti-TNF-α) biologics are efficacious to induce and maintain remission in adult and pediatric Crohn's disease (CD) and are widely used worldwide.[1–3] Infliximab (IFX), a chimeric anti-TNF-α antibody and Adalimumab (ADA), a humanized anti-TNF-α agent are recommended in the management of pediatric CD.[4,5]

For many years, IFX was the first choice in pediatric patients with moderate to severe CD after failure of immunosuppressants. ADA is more recently used and usually prescribed as a second line therapy in patients with loss of response (LOR) or intolerance to IFX. Because of its ease of use at home with subcutaneous (SC) injections and its rapid effectiveness, ADA is now often used as a first-line treatment especially in children.

Despite a good efficacy of anti-TNF-α, LOR is a major concern in inflammatory bowel diseases (IBD) management, as it occurs within 1 year in an estimated 13% of patients treated with IFX and 20% of patients treated with ADA.[6,7] One-third of the patients do not respond to induction therapy (i.e., primary nonresponders) and approximately 50% of initial responders lose response along time (i.e., secondary LOR).[5] The LOR, whether initial or late, may be due to an immunogenic effect (presence of antidrug antibody), pharmacokinetic effect (low trough concentrations without antidrug antibody) or pharmacodynamic (adequate trough concentrations) effect.[5] Management of patients with low or nonresponse to anti-TNF-α is challenging for pediatricians since they are the only biotherapies authorized in this population. Therapeutic drug monitoring (TDM), defined as the measurement of drug concentrations and anti-drug antibody, is an important tool for optimizing biologic therapy. For example, patients with LOR due to low trough levels without antibody will benefit from increased doses. The recent ECCO-ESPGHAN guidelines recommend that patients with pharmacodynamic LOR that is, well in rang trough levels should be switched to an out-of-class biologic.[5] Other biotherapies targeting different inflammatory pathways such as vedolizumab or ustekinumab have been developed for several years in adults and have proved their efficacy to induce and maintain remission.[8,9] Ustekinumab and vedolizumab are also efficacious in pediatric CD,[10–12] but they are still used off-label in pediatric CD patients as long-term data are still lacking. The place of the different biotherapies remains to be defined.

What is New?

- We demonstrated the efficacy of IFX as second line therapy after loss of response (LOR) or intolerance to ADA in pediatric CD patients at 1 year.
- IFX could be an interesting therapeutic choice in patients experiencing LOR to ADA before switching for another class of biotherapy.

What is Known?

- Adalimumab (ADA) and Infliximab (IFX) are recommended for induction and maintenance of remission in pediatric Crohn's disease (CD).
- Currently ADA is often used as first line therapy.

The aim of our study was to describe disease outcome at 1 year in pediatric CD patients who started with SC ADA and were subsequently switched to intravenous (IV) anti-TNF-α (IFX).

2 | MATERIAL AND METHODS

2.1 | Study design

A multicenter retrospective cohort study was conducted among French pediatric gastroenterology centers, members of the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du tube Digestif Pédiatrique (GETAID pédiatrique) in France. The GETAID pédiatrique is a collaborative nationwide research network on pediatric IBD in France. All centers of the "GETAID pédiatrique" were contacted and asked to complete a standardized and detailed questionnaire if they had patients who fulfilled the inclusion criteria.

All patients aged under 18 years with CD who had been treated with IFX after failure of ADA were eligible for this study. Data were collected over a 3-year period, between April 1, 2019 and April 1, 2022. Patients were included in the study if they had a confirmed diagnosis of CD, a follow-up of more than 3 months since diagnosis, and if they had been treated as first line therapy with ADA with a switch to IFX due to ADA failure, occurrence of side effects or a LOR.

Patients with ulcerative colitis (UC) or IBD unclassified were excluded from the study, as well as patients treated with another biotherapy after failure of ADA.

2.2 | Outcomes

The primary outcome was sustained corticosteroid (CS) free clinical remission at 1 year of IFX treatment. Weighted Pediatric CD Activity Index (wPCDAI) was used to assess disease activity at diagnosis and during follow-up.[13,14] Clinical remission was defined by a wPCDAI disease activity score less than 12.5 points[13] and no treatment with CS.

Secondary outcomes were CS free clinical remission rate at 6 months, clinical response rate at 6 and 12 months, defined as a wPCDAI disease activity score drop of at least 17.5 points, and biological remission rate, defined by normalization of serum albumin (>35 g/L), C-reactive protein (CRP) (<5 mg/L) and erythrocyte sedimentation rate (ESR) (<10 mm) at 6 and 12 months.

2.3 | Data collection

The diagnosis of CD needed to meet the revised Porto Criteria and included clinical history, physical examination, and endoscopic, histological and radiological findings.[15] Demographic

data included sex, age at diagnosis, referral center of the patient. Disease location and disease behavior were classified according to the Paris classification.[16]

Data were collected regarding ADA treatment: indication, date of first injection, total duration (months), optimization during follow-up (increase of dosage or decrease of interval between injections), immunization, trough concentrations if available and finally the reason for discontinuation of ADA (LOR, side effects, immunization…).

We also noted data about IFX treatment: date of first injection, initial induction scheme, maintenance scheme (doses and infusion intervals), optimization of IFX and concomitant immunosuppressive therapy (Azathioprine, 6-mercaptopurine, and Methotrexate).

At diagnosis and every 6 months during follow-up, clinical (wPCDAI, anthropometric data), biological and therapeutic parameters were collected. Laboratory parameters included inflammatory markers (ESR and CRP), nutritional parameters (albumin), fecal calprotectin and anti-drug antibodies. We also noted the occurrence of complications such as disease flare, hospitalization, perianal or intra-abdominal abscess, fistula, need for surgery, serious infection, and any other side effect attributed to IFX.

For patients in whom IFX was stopped during the study and who therefore left the protocol, we analyzed the cause of treatment discontinuation, the total duration of IFX, and we also collected the current maintenance treatment.

The patients still treated with IFX at M12 were divided in two groups: the first group, « responder » patients, defined by clinical-biological remission (CS free clinical remission and wPCDAI score < 12.5 points at M12 under IFX), and the second group of « non-responders » patients (no remission under treatment). These two groups were compared on clinical and biological criteria at diagnosis and at initiation of IFX to individualize prognostic factors of response to IFX.

2.4 | Statistical analysis

Qualitative variables were described with frequencies and percentages. Quantitative variables were expressed as mean and standard deviation. We compared two groups of patients: the « IFX responders» and the « non-responders». Chi-square tests with Fisher correction were used to address any differences for categorical variables, as needed. A Wilcoxon test was used to compare quantitative variables between those two groups. The statistical tests were conducted over the medians, due to small study samples and non-normal distribution of data. A p Value less than 0.05 was defined as statistically significant. Statistical analyses were performed using SAS software version 9.4. The data

underlying this article will be shared on reasonable request to the corresponding author.

3 | RESULTS

3.1 | Patients' characteristics

Between April 1, 2019, and April 1, 2022, 32 patients from 12 out of the 39 « GETAID pédiatrique » centers in France, were included in the study.

Patients' characteristics at inclusion are presented in Table 1. Mean age at diagnosis of CD was 12.2 ± 2.5 years. Most patients had ileocolonic involvement (43.8%) and inflammatory phenotype B1 (30 patients, 93.8%). Four patients (12.5%) had a perianal disease at diagnosis. Two third of the patients (68.8%) presented with growth impairment at diagnosis.

In 21 patients (65.6%) ADA was introduced due to active CD despite previous treatments. Other indications for ADA were the presence of severe ileocecal CD at diagnosis in nine patients (28.1%), CS dependency in three patients (9.4%), or the presence of side effects in previous treatments in one patient (3.1%). Mean age at first injection of ADA was 13.3 ± 2.7 years. Twenty-nine patients underwent drug optimization: 11 patients (34.4%) needed a dose increase regimen, and 18 (56.3%) a reduction

TABLE 1 Patients characteristics.

Patients	Total ($n = 32$)
Baseline (at CD diagnosis)	
Sex ratio (M/F)	1
Age at diagnosis (year, mean ± standard deviation)	12.2 ± 2.5
Disease location (n, %)	
L1	11 (34.3%)
L2	7 (21.9%)
L3	14 (43.8%)
L4a	8 (25%)
L4b	0 (0%)
Phenotype (n, %)	
B1	30 (93.8%)
B2	9 (28.1%)
B3	1 (3.1%)
Perianal disease at diagnosis (*n*, %)	4 (12.5%)
Growth impairment (*n*, %)	22 (68.8%)
At initiation of ADA	
Age at introduction of ADA (years, mean ± standard deviation)	13.3 ± 2.7
ADA increase dosage (*n*, %)	11 (34.4%)
Increased frequency of ADA injections (*n*, %)	18 (56.3%)
Presence of antibodies against ADA (*n*, %)	3 (11.1%)
Duration of ADA treatment (months, mean ± standard deviation)	16.1 ± 15.4
At initiation of IFX	
Duration of CD at M0 of IFX (years, mean ± standard deviation)	2.5 ± 1.5
Age at introduction of IFX (years, mean ± standard deviation)	14.6 ± 2.4
Combotherapy with IFX (AZA, 6-MP or MTX) (*n*, %)	26 (81.3%)
Induction scheme (n, %)	
5 mg/kg at W0-W2-W6 (Conventional)	21 (66%)
10 mg/kg at W0-W2-W6	10 (31.3%)
5 mg/kg W0-W2-W4-W6	1 (3.1%)

Note: The results of the qualitative values are expressed as the mean, with its standard deviation.

of intervals between doses (weekly). The mean duration of ADA was 16.1 ± 15.4 months. Twenty-five patients (78%) received ADA on monotherapy without immunosuppressant. For 11 (34%) patients, ADA trough level was available at time of the switch. Mean trough level was 12.2 ± 7.8 µg/mL. Eight patients among this subgroup had trough levels higher then 7.5 µg/mL and three patients with low trough level developed ADA antibodies at the end of the treatment.

ADA was discontinued due to LOR in 17 patients (53.1%), partial response in 13 patients (40.6%) and primary nonresponse in two patients (6.3%). No patient stopped ADA due to side effects.

At first IFX infusion, the mean duration of the disease was 2.5 ± 1.5 years with a mean age of the patients of 14.6 ± 2.4 years. Twenty-six patients (81.3%) were on concomitant medical therapy during IFX treatment (AZA, 6-MP, or MTX). The IFX induction scheme was conventional for most patients, that is, 5 mg/kg at Weeks 0, 2, and 6 (21 patients, 66%). Nine patients (28.1%) had an induction scheme of 10 mg/kg of IFX, while the others (23 patients, 71.9%) had received 5 mg/kg.

3.2 | Outcomes

The flow chart is shown in Supporting Information Data, (Figure 1). At the end of IFX induction scheme, one patient discontinued IFX due to primary nonresponse to IFX and need for urgent surgery. At 6 and 12 months, 29 (90.6%) and 27 (84.4%) patients respectively were still treated with IFX. Five patients (15.6%) were switched out of class and treated with another biotherapy.

3.2.1 | Clinical remission

At M12, among the 27 patients still treated by IFX, 22 (81.5%) were in CS free clinical remission, 1 (3.7%) had a significant therapeutic response to IFX and 4 (14.8%) had no response. Finally, CS free clinical remission rate was 68.7% (22 patients out of 32). Four patients (12.5%) were on concomitant partial EEN with IFX and two patients (6.2%) received steroids.

Induction of clinical remission at W10 (1 month after the end of IFX induction scheme) was obtained in 11 patients, while nine patients showed a clinical response. One patient was nonresponder to IFX induction therapy. Dosing of IFX was 6.2 ± 4.2 µg/mL.

At M6 of IFX therapy, 29 patients (90.6%) were still treated with IFX, with 16 patients (55.2%) in CS free clinical remission and six patients (20.7%) with a significant therapeutic response. Seven patients (24.1%) were nonresponder to IFX, although treatment was pursued. Three patients (9.4%) were no longer treated with IFX (Figure 1).

3.2.2 | Biological response

Along time, we observed a decrease of inflammatory parameters as shown in Figure 2. CRP decreased from 20.8 ± 33.4 mg/L at M0, to 3.3 ± 6.4 mg/L at M12 ($p = 0.12$), while the ESR decreased from 42.7 ± 37.9 mm/h to 18.4 ± 21.8 mm/h at M12 ($p = 0.02$). The albumin increased from 34.8 ± 6.0 g/L at M0, to 41.1 ± 3.9 g/L at M12 ($p = 0.018$). Those results are statistically significant between M0-M6 and M0-M12. Under IFX, the wPCDAI decreased over time (47.5 ± 24.1, 16.6 ± 21.2 and 9,7 ± 19.0) at M0, M6 and M12 respectively ($p < 0.001$ for M0-M6 and M0-M12, $p = 0.03$ for M6-M12) (Figure 2).

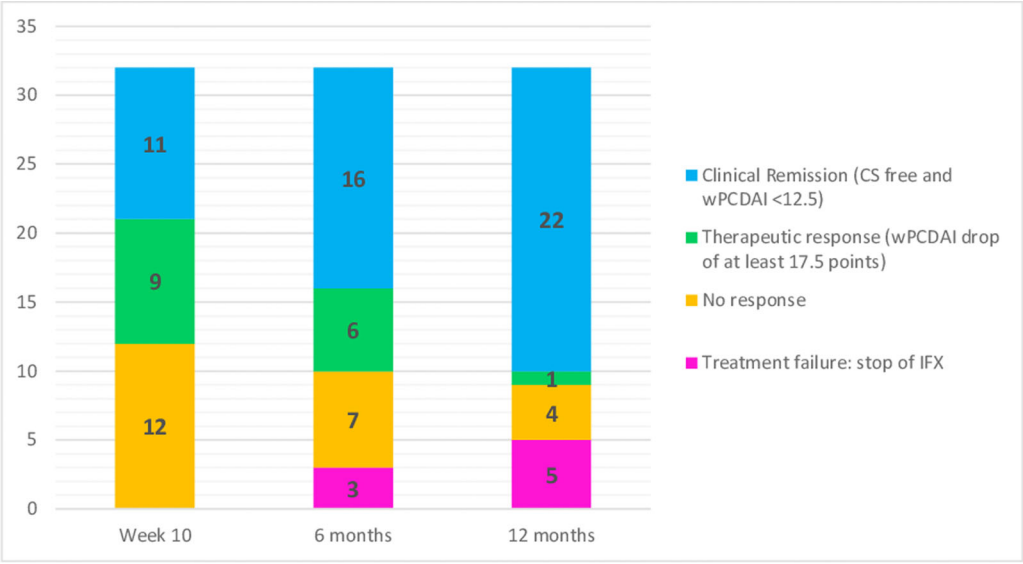

FIGURE 1 Response to IFX treatment at 10 weeks, 6 months and 12 months. IFX, infliximab.

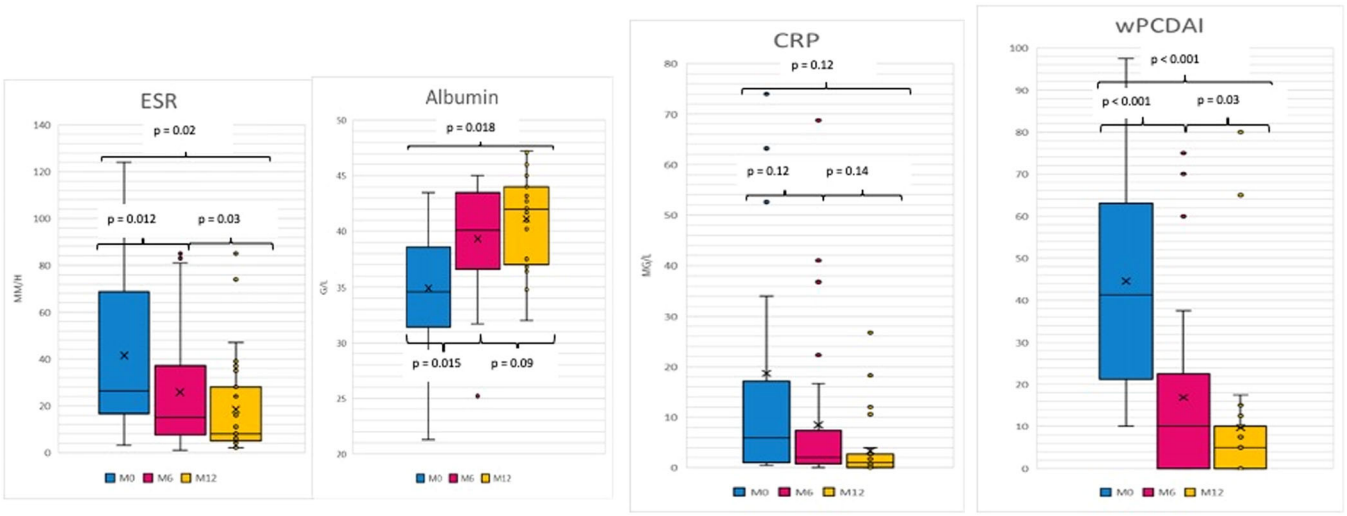

FIGURE 2 Comparison of clinical and biological parameters in patients under IFX at 0, 6, and 12 months. IFX, infliximab.

Patient weight improved significantly over 12 months of IFX while height remained stable (Table S1).

Nine (28.1%) patients were optimized during follow up with increase of the doses of IFX from 5 to 10 mg/kg. No patient developed antibodies against IFX during follow-up. The mean IFX trough level was 8.0 ± 5.2 µg/mL at M6 and 8.5 ± 5.4 µg/mL at M12. The mean interval between IFX infusions was 5.0 ± 1.4 weeks at M6 and M12. It was necessary to decrease intervals between infusions in three patients (10.3%) at M6 and four patients (14.8%) at M12.

Complications during IFX treatment (relapse, surgery, hospitalization, abscess, serious infection, side effect [infusion reaction, skin adverse event…]) were rare, concerning five patients over 29 (17.2%) at M6 and four patients over 27 (14.8%) at M12,3 of whom already had complications at M6.

Abscesses occurred in four patients (13.8%) within 6 months: three patients developed perianal abscesses, and one patient had intra-abdominal abscess of the terminal ileum. Surgery was required within the first 6 months of IFX in two of these patients (6.9%). One patient underwent resection of distal ileum due to an abscess, and the other had a surgical drainage of perianal lesion.

At M12 we observed a fistula closing in one patient with perianal disease, but the two other ones had persistent active perianal disease.

One patient experienced a relapse at M6, and one other at M12 (3.4% and 3.7% respectively).

No serious infection nor treatment-related side effect during follow-up were reported.

3.3 | Comparison of responders and nonresponder patients at M12

Among the 27 patients still on IFX at M12, 22 patients (81.5%) were responders, and five patients (18.5%) were nonresponders. The comparison of these two groups is presented in Table 2. There was no difference between both groups regarding sex ratio, disease location and phenotype. Nonresponder patients (three patients out of five) had significantly more perianal disease at the initiation of IFX than responders (two patients out of 22) (60% vs. 9%; $p = 0.03$). Twenty-one (65.6%) patients on IFX had measurement of TDM during treatment. Responders had significantly higher IFX trough levels at M6 than non responders (9.1 µg/L ± 5.3 vs. 3.6 ± 2.5; $p = 0.04$).

In patients for whom ADA was discontinued due to a secondary LOR ($n = 17$), there were 42.9% and 92.3% of patients responding to IFX at M6 and M12, respectively. When ADA was stopped in case of partial but insufficient response ($n = 13$), 69.2% and 66.7% of patients were responders to IFX at M6 and M12, respectively. Finally, in case of discontinuation of ADA for primary nonresponse ($n = 2$), 50% and 100% of patients were responders to IFX at M6 and M12, respectively (2 patients). The duration of ADA treatment tended to be shorter in the responder group ($n = 22$) versus nonresponders ($n = 5$), but it was not statistically different (13.3 ± 10.2 months in the responder group vs. 24.8 ± 30.3 months in the nonresponder group). Three patients out of 5 on the nonresponder group and eight patients out of 22 in the responder group had data regarding ADA trough level. In the eight patients' responder to IFX, their median ADA trough level was 12 µg/mL,[1–27] with a trough level less than 7.5 in only one patient. On the contrary the three nonresponder patients had median trough level of 6.3 µg/mL (2.7–18.5); one of the three patients had a rate > 7.5 µg/mL.

Mean IFX trough level at the end of the induction scheme was higher in responders than in nonresponders (6.7 ± 3.8 µg/mL vs. 4.5 ± 6.3 µg/mL), but it did not reach statistical significance due to the small sample size. At M12, mean trough level was 9.1 ± 5.7 µg/mL and 6.1 ± 3.7 µg/mL in responders and nonresponders respectively ($p = 0.38$).

TABLE 2 Comparison of responders and nonresponders to Infliximab at M12.

Patients	Responders ($n = 22$)	Nonresponders ($n = 5$)	p Value
Sex ratio (M/F)	1	0.7	1.0
Disease location (n, %)			
L1	6 (27.3%)	3 (60%)	0.29
L2	6 (27.3%)	0 (0%)	NA
L3	10 (45.4%)	2 (40%)	1.0
Phenotype (n, %)			
B1	21 (95.5%)	4 (80%)	0.34
B2	5 (22.7%)	2 (40%)	0.58
B3	0 (0%)	1 (20%)	NA
Perianal disease at CD diagnosis (n, %)	3 (13.6%)	1 (20%)	1.0
Perianal disease at the end of induction (n, %)	2 (9%)	3 (60%)	0.03
Failure to thrive at diagnosis (n, %)	15 (68.2%)	2 (40%)	0.32
Duration of ADA treatment (months, mean ± SD)	13.3 ± 10.2	24.8 ± 30.3	0.97
Combotherapy (AZA, 6-MP or MTX) (n, %)	19 (86.4%)	2 (40%)	0.06
Duration of CD at M0 (years, mean ± SD)	2.3 ± 1.3	2.8 ± 2.2	1.0
Trough level of Infliximab at the end of induction (µg/mL µg/mL, mean ± SD)	6.7 ± 3.8	4.5 ± 6.3	0.15
Trough level of Infliximab at M6 (µg/mL, mean ± SD)	9.1 ± 5.3	3.6 ± 2.5	0.04
Trough level of Infliximab at M12 (µg/mL, mean ± SD)	9.1 ± 5.7	6.1 ± 3.7	0.38
CRP at M0 (mg/L, mean ± SD)	17.8 ± 27.6	33.9 ± 54.6	0.30
ESR at M0 (mm/h, mean ± SD)	36.1 ± 32.9	71.4 ± 48.9	0.12
Albuminemia at M0, (g/L, mean ± SD)	35.8 ± 5.4	30.5 ± 7.4	0.15
wPCDAI at M0, (mean ± SD)	44.8 ± 21.4	59.5 ± 33.9	0.37
Change in weight M0-M12 (SD)	−1.03 ± 1.5	0.3 ± 1.9	0.007
Change in height M0-M12 (SD)	−0.5 ± 1.2	−0.2 ± 1.2	0.07

Note: The results of the qualitative values are expressed as the mean, with its standard deviation.

The use of combination therapy with an immunosuppressant was associated with a better response to IFX: 86.4% of responders ($n = 19$) were under combotherapy, while only two patients (40%) of nonresponders ($p = 0.056$). Half (50%, $n = 11$) of responders were optimized (increase IFX doses and/or closer infusions) at M6 and 31.8% (seven patients) at M12, while among the five nonresponder patients at M12, two patients (40%) were intensified at M6 and three patients (60%) at M12.

Inflammatory parameters tended to be higher in nonresponders versus responders, although this difference was not significant (Table 2).

3.4 | Outcome of patients who failed IFX

Among the 32 patients included in our study, five patients (15,6%) were no longer on IFX at M12. Five patients were switched before M6. One patient stopped IFX due to clinical worsening despite IFX medication, two other patients underwent surgery, one patient had a CD severe complication (abscess), and one patient did not reach mucosal healing during the follow-up. Currently, two of these patients are successfully treated with ustekinumab, two with ADA and one with vedolizumab.

4 | DISCUSSION

The aim of our study was to investigate disease outcome of pediatric CD patients who started with SC anti-TNF-α (ADA) and subsequently switched to IV anti-TNF-α (IFX). We were able to show that a large number of pediatric CD patients (68.7%) who switched to IV therapy with IFX after ADA failure could be maintained in remission at 1 year with 84.4% of our patients still on IFX at 1 year, among which 81.5% of them were in clinical and biological remission. Only a small proportion of patients failed IFX during the 12

months follow-up. IFX therefore appears to be an effective second-line treatment after failure of ADA.

To our knowledge, this is the first report evaluating the efficacy and outcome of pediatric CD patients switched from SC to IV anti-TNF-α treatment. Few studies are published on this topic in adult CD and UC patients. Historically, IFX was used as a first line treatment with a switch to SC anti-TNF-α biotherapy in case of IFX failure. With increasing use of first line SC anti-TNF-α, IFX tends to be reserved for severe or refractory disease. In case of LOR to SC anti-TNF-α, patients are usually switched to another class of biologics.[5] Indeed, the switch from SC to IV anti-TNF-α is not very common, which explains why we have only a few cases reported, even though we contacted all the French pediatric IBD centers in the "GETAID pédiatrique."

In 2018, Peeters et al conducted a prospective, observational, multicentric cohort study, including 21 adults with CD who had failed ADA.[17] Remission was obtained in 25% of patients at 6 months after the switch with a median IFX trough level within the therapeutic objectives (5 µg/mL), and 20% at 12 months, with a median trough level below the therapeutic objectives (3.4 µg/mL).[17] The differences with our study may be explained by a smaller sample size in their study, a lower IFX trough level, or a poorer response of adults to biotherapies. Indeed, the response to biotherapies is particularly excellent in children, probably due to the shorter duration of the disease. In contrast, in this study, IFX was maintained in 81% patients at M12, a proportion similar to ours.[17] Mizoshita et al. in 2016, showed that 17.6% of patients treated with ADA were switched to IFX due to ADA failure, and had maintained prolonged remission after intensifying IFX.[18] Grau et al, who studied the efficacy of a second anti-TNF-α after failure of a first one, showed that 76%, 68% and 64% of their patients were in remission at M12, M18 and M24 respectively, a proportion which is similar to our results.[19] Gagnière et al, in 2015, studied the efficacy of retreating with IFX 61 adults with CD who had failed IFX and then ADA.[20] This study showed that 42% of patients were in remission 6 to 8 weeks after re-induction of IFX, a proportion similar to what we found, and this remission was predictive of a long-term therapeutic response ($p = 0.006$).[20] A short interval between the first and second treatment with IFX was predictive of a better response to the second IFX line ($p = 0.017$).[20]

In UC, there has been one study on SC/IV anti-TNF-α switch in adults.[21] Clinical remission at 12 months was achieved in up to 77% of patients who stopped the SC agent for LOR, and in up to 47% of patients who discontinued ADA or golimumab (GOL) due to primary nonresponse.[21] The overall remission rate was 50%.[21] Since ADA has just recently been authorized for UC in children, there is no pediatric study on the efficacy of IFX after ADA failure in children with UC. Second-line treatment with IFX after a first anti-TNF-α therefore appears to be an attractive option in adult and pediatric patients with CD before considering a different therapeutic class.

To highlight prognostic factors that could explain success or failure of IFX, we compared responder and nonresponder patients. Our results showed a better response in patients receiving combotherapy, although this result was not statistically significant ($p = 0.056$). A study in adults with CD failing IFX then ADA with reintroduction of IFX showed that concomitant immunosuppressive therapy with IFX was a predictor of longer efficacy of IFX.[20]

The reason why ADA is stopped appears to influence the response to IFX. In UC patients, Viola et al showed that patients who switched for LOR had better clinical remission rates than patients who switched for primary failure, also it was not statistically significant.[21] A systematic review including 46 studies (37 for CD, 8 for UC, and 1 for pouchitis) investigated the efficacy of a second anti-TNF-α after failure of the first.[22] The remission rate was higher when the reason to withdraw the first anti-TNF-α is intolerance (61%), compared with secondary (45%) or primary failure (30%).[22] An observational study, conducted in Spain in 2012 which included 15 adults with CD under IFX after failure of ADA also showed that response was better in patients for whom ADA was stopped in case of LOR or side effects, compared to those with primary nonresponse to ADA.[23] Thus, the efficacy of a second anti-TNF-α in IBD patients largely depends on the reason for switching. IFX appears to be a good therapeutic alternative to ADA in adults with CD in whom ADA has been stopped in case of LOR or side effects.[23] On the contrary, in case of primary nonresponse to ADA, it seems better to use another class of biotherapy.[23] With only two patients with primary nonresponse to ADA in our cohort, we can't conclude on this point. Children with LOR or partial response to ADA seems to have greater clinical remission rate with IFX. One explanation for such differences could be drug trough levels. Low trough level is associated with decreased therapeutic response.[24] Some studies highlighted that children need higher trough level to obtain remission.[5,25] We can hypothesize that some children had primary nonresponse to ADA due to low trough level. The switch to IV IFX with better dosage calculated with the children's weight could help to have higher therapeutic trough level and then better response to anti-TNF-α. Drug trough levels are different between IV and SC administration. For ADA, recommended trough levels are higher than those recommended for IFX.[5] Indeed, pharmacokinetic of anti TNF drugs are different between IV and SC. With SC ADA there are slow absorption rate following administration, slow elimination rate, and uniform concentration-time profiles at steady state.[26] In contrast, with IFX's IV administration, there are high loading doses, high maintenance doses with very high peaks and low minimums and hence high peak-to-trough ratios. For the 5 and 10 mg/kg IFX infusions, these ratios grow to about 20 and 40 times for ADA,

respectively. Such differences in pharmacokinetics over time could explain better response with IV IFX in our patients. Interestingly, we observed that children with LOR to ADA with adequate trough level (>7.5) better respond to IFX than the others may be due to differences in pharmacokinetic of the drugs. This is a very important result for clinical practice.

In the literature, intensification of IFX treatment is observed in half of adults with CD at 6 months, and 75% of patients at 12 months.[17] Another study showed that IFX was intensified in one-third of patients, achieving or regaining remission in 37% of patients.[19] Children are often escalated and sometimes earlier than adult. Jongsma et al even suggested intensification of the induction scheme in children younger than 10 years to optimize clinical response.[25]

In our study, the presence of perianal disease at the end of induction with IFX, a known criteria for CD severity,[5,27] was much more frequent in the nonresponder group than in responders (60% vs. 9%, $p = 0.03$). A retrospective, multicenter study from 2016 supports our results: the rate of remission was lower in patients for whom anti-TNF-α was introduced due to a perianal disease ($p = 0.005$).[19]

We also showed that responders exhibited lower inflammatory markers at baseline than nonresponders. These results are not significant, probably due to a small sample size. We can hypothesize that lower inflammatory markers could reflect milder disease thus leading to better response to IFX. Patients with very severe CD (perianal disease, inflammatory phenotype, etc.) are more difficult to control, due to a poorer response to biotherapies, and practitioners should consider a more aggressive therapeutic approach using a "Top-Down" strategy.

Although the results were not statistically significant, our study found that nonresponders had lower IFX trough levels than responders over time. This is probably one of the reasons of lack of response to IFX and lead to therapeutic issues by optimizing doses and intervals of IFX infusions.

One of the barriers to the switch from SC to IV infusion is the need for hospitalization. To improve the patient's quality of life, IFX in a SC form is currently used in adult population. In 2021, Schreiber et al conducted a multicentre randomized controlled trial of noninferiority in 131 adults to compare the IV and SC forms of IFX in the treatment of IBD.[28] The authors showed that the SC form is noninferior to the IV form, and that IFX trough levels are even higher with the SC form, and higher than the therapeutic targets for the IV form (>5 µg/mL).[28] It is therefore possible to make a place in the future for IFX in SC injections after failure of ADA in children.

In our study, we observed that over time, some patients failed IFX, and required a switch to another biotherapy, such as vedolizumab or ustekinumab.

We believe that it is necessary to pursue this study on a larger scale, and to assess the efficacy of the switch to define the exact place of each treatment. It would be interesting to stratify patients on their pharmacokinetic of ADA and especially to study the sub population of patients failing ADA with adequate trough level to decipher if those patients should be switch to IFX or out of class with another biologic. Our study on very few data suggests that those patients with adequate trough level of ADA could respond to IFX but more studies are needed to conclude.

Our study has some limitations: it is an observational, retrospective study with a small number of patients. However, our study is the first to investigate the switch from ADA to IFX in children with CD. Even though we only have a small sample size, our study is multicentre and exhaustive since it included all French pediatric centers. We were only able to include 32 patients across France, which suggests that this therapeutic switch still concerns few patients.

5 | CONCLUSION

The results of our study show that the switch from SC ADA to IV IFX is effective, allowing to obtain a clinical remission at 1 year in up to 70% of patients with decrease of inflammatory markers. This therapeutic strategy is therefore a good alternative in case of ADA failure, whatever the reason of discontinuation of ADA. IFX remains a treatment to consider for a patient who has failed ADA before switching to a new therapeutic class, such as ustekinumab or vedolizumab.

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CONFLICT OF INTEREST STATEMENT

Claire Dupont: has received consultant fees from ABBVIE. Frank M. Ruemmele received consultation fee, research grant, or honorarium from Janssen, Pfizer, Abbvie, Takeda, Celgene, Nestlé Health Science, Nestlé Nutrition Institute. Bénédicte Pigneur has served as a speaker and a consultant member for Abbvie and Amgen. The remining authors declare no conflict of interest.

ETHICS STATEMENT

Patients and parents gave their informed consent for participation in this study. The study was approved by the "Groupe Français d'Hépatologie Gastro-entérologie et Nutrition Pédiatrique" (GFHGNP) Review Boards (n°2022-039) for the ethical approval and the French national data protection agency (Commission nationale de l'informatique et des libertés n°2222662 v 0).

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