# Ustekinumab Use in Pediatric Inflammatory Bowel Disease: A French Multicenter Study From the Pediatric GETAID

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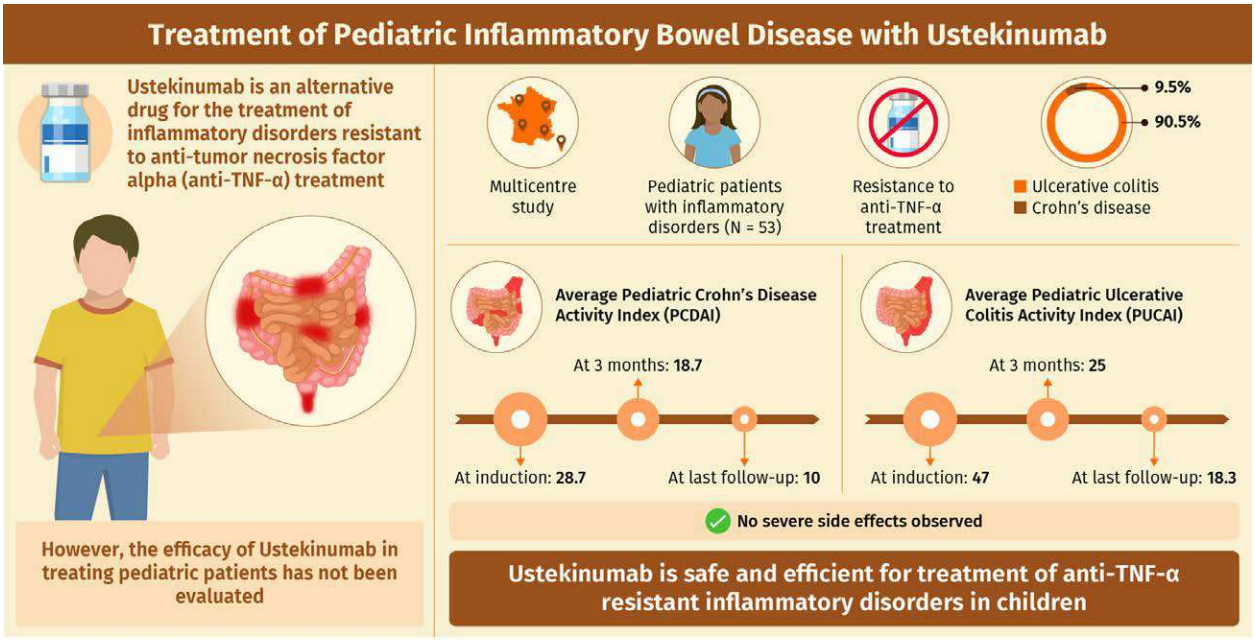


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**ABSTRACT**

**Objectives:** Ustekinumab is known to be efficient in adult patients suffering from moderate to severe Crohn disease (CD) and ulcerative colitis (UC) resistant to anti-tumor necrosis factor-alpha (TNF-α). Here, we described the clinical course of treatment with ustekinumab in French pediatric inflammatory bowel disease (IBD) patients treated with ustekinumab.

**Methods:** This study includes all pediatric patients treated by ustekinumab injection for IBD (CD and UC), between January 2016 and December 2019.

**Results:** Fifty-three patients were enrolled, 15 males and 38 females. Forty-eight patients (90%) had a diagnosis of CD and 5 (9.4%) had UC. Sixty-five percent of CD patients presented an ileocolitis. Perineal disease was observed in 20 out of 48 CD patients (41.7%), among them 9 were treated surgically. All patients included were resistant to anti-TNF-α treatment.

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**What Is Known**

- Ustekinumab is known to be efficient in adult patients suffering from moderate to severe Crohn disease (CD) and ulcerative colitis (UC) resistant to anti-tumor necrosis factor-alpha (TNF). However, studies evaluating ustekinumab in pediatric inflammatory bowel disease (IBD) are scarce.

**What Is New**

- This study provides a real-life experience of ustekinumab therapy in more than 50 IBD children, CD and UC, from nine university hospitals of the "pediatric GETAID" consortium, in France. Ustekinumab is a safe and efficient therapy strategy for anti-TNF-α resistant pediatric CD and UC.

Fifty-one percent had presented side effects linked to anti-TNF-α, including psoriasis and anaphylactic reaction. The average Pediatric Crohn Disease Activity Index (PCDAI) at induction was 28.7 (5–85), 18.7 (0–75) at 3 months of treatment and 10 (0–35) at the last follow-up. The average Pediatric Ulcerative Colitis Activity Index at induction was 47 (25–65), 25 (15–40) at 3 months of treatment and 18.3 (0–35) at the last follow-up. No severe side effects were observed.

**Conclusion:** In this retrospective, multicentral study, ustekinumab proved to be efficient in pediatric patients resistant to anti-TNF-α. PCDAI has been significantly improved in patients with severe disease, treated with ustekinumab.

**Key Words:** GETAID pédiatrique, pediatric inflammatory bowel disease, ustekinumab

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Pediatric inflammatory bowel disease (IBD) treatment is challenging mainly due to an early onset of the disease in children. Enteral nutrition was recommended by European Society for Paediatric Gastroenterology, Hepatology and Nutrition/European Crohn and Colitis Organization guidelines as first line therapy in mild to severe luminal Crohn disease (CD). Biotherapy has already been used to treat relapsed and refractory patients since 2000. Indeed, anti-tumor necrosis factor-alpha (TNF-α) agents, such as infliximab, have completely changed the natural course of the disease (1). Although the initial response to infliximab is generally excellent, studies have shown that about one-third of these patients did not respond to the treatment during the first year of therapy (2).

Intestinal inflammation is linked to homeostasis alteration. Strong evidence suggests a key role of adaptive immunity (3). Indeed, among several complex mechanisms, Th17 has emerged as one of the main T helper lymphocytes subset involved in IBD (4,5). Moreover, genome-wide association studies suggested protective polymorphism (uncommon coding variant rs11209026, c.1142G>A, p.Arg381Gln) on receptor IL23-R linked to CD (6,7). Th17 massively infiltrates the inflamed intestine of patients with IBD and produces IL23, a proinflammatory cytokine, which results in intestinal damage (8).

Ustekinumab is a monoclonal antibody targeting IL-12 and IL-23 common p40 subunit (9). UNIT-I study has reported a 30% remission in CD adult patients resistant to anti-TNF-α. Moreover, a recent study, UNIFI showed 40% remission in ulcerative colitis (UC) anti-TNF-α resistant patients (10). Ustekinumab is approved by the European Union and the United States for treatment in adult patients with moderate to severe refractory CD and UC or with intolerable side effects caused by corticosteroids, immunomodulators, or TNF-α antagonist.

In France, ustekinumab has been approved for the treatment of children with moderate-to-severe psoriasis (11). However, data on efficacy and tolerance of ustekinumab in pediatric IBD are scarce.

In this study, patients with pediatric IBD in France, treated with ustekinumab, were clinically and biologically characterized. Effectiveness and tolerance results of the treatment were also reported.

## MATERIALS AND METHODS

### Study Design

This retrospective and multicentral study was conducted between January 2016 and December 2019. Nine, French hospital medical centers, members of the Groupe d'Etudes Therapeutiques des Affections Inflammatoires du tube Digestif Pédiatrique (GETAID pédiatrique), participated in this study: Paris (Necker and Robert-Debré hospitals), Amiens, Bordeaux, Le Havre, Rennes, Strasbourg, Tours and Lyon. A retrospective chart review was performed based on the electronic medical chart for patients' baseline characteristics, clinical data, clinical disease activity index, disease phenotype before starting ustekinumab (based on Paris classification for CD patients (12)), treatment history, endoscopic findings, and laboratory parameters at the beginning of the treatment (induction), 3 months after induction, and at the last follow-up. A growth delay at diagnosis was defined by at least 1 of the following criteria: (i) height *z* score at diagnosis or subsequently significantly less than expected height *z* score and (ii) current height *z* score significantly less than height *z* score at diagnosis (12).

All patients with IBD followed in the mentioned hospitals and receiving treatment with ustekinumab were identified and included in this study. Patients had to be ≤18 years old at the induction to fall into the inclusion criteria. There was no other exclusion criteria.

### Study Variables

Baseline characteristics included: demographics (age, sex), diagnosis date and disease duration, weight and height, behavior and location, extra-intestinal symptoms, treatment history (infliximab, adalimumab, other anti-TNF-α, 5-aminosalicylic acid, corticosteroids, immunomodulators), adverse effects, and surgery.

The disease activity was measured by the Pediatric Crohn Disease Activity Index (PCDAI) for CD (13) and the Pediatric Ulcerative Colitis Activity Index (PUCAI) for UC (14) during the follow up by the clinician or was calculated retrospectively. When disease activity score was missing, it was calculated during data collection at each follow-up point, when data were available. PCDAI was ranged between remission (<10), mild (<30), moderate (≥30–40), and severe (≥40) disease. A score change of ≥12.5 points reflects clinically significant response to therapy (15). The PUCAI maximum score was 85, with remission defined as a score <10, mild disease score between 10 and 35, moderate disease score between 40 and 60, and severe disease score between 65 and 85.

Biological data included C-reactive protein (CRP, mg/L) (N < 5 mg/L), erythrocyte sedimentation rate (ESR, mm) (N < 15 mm), hematocrit (%) (35%–50%), serum albumin (g/L) (35–50 g/L), and fecal calprotectin (N < 50 μg/g) when available.

In case of endoscopic evaluation concomitant to a follow up, the endoscopic findings were collected: inflammation, ulceration, and endoscopic activity score.

Common adverse effects described with ustekinumab were also collected: fatigue, anaphylaxis, arthralgia, dizziness and



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TABLE 1. Baseline characteristics, Paris classification, biological parameters, and treatments parameters at induction

| Baseline characteristics | |
|---|---|
| Gender (M/F) | 15/38 |
| Age at diagnosis, y | 9.8 (2.3–16) |
| Disease duration, y | 6.7 (1.1–13.6) |
| Age at induction, y | 15.03 (8.7–18) |
| Diagnosis | |
| CD | 48 (90.6%) |
| UC | 5 (9.4%) |
| Weight, kg | 44.9 (21.5–70.5) |
| BMI, kg/m$^2$ | 19.0 (13.1–32.6) |
| Extra-intestinal manifestations (n = 53) | 15 (28.3%) |
| Rheumatologic | 9 (18.8%) |
| Hepatic | 2 (4.2%) |
| Dermatologic | 6 (12.2%) |
| Previous surgery (n = 41) | 9 (22%) |
| **Paris classification for CD** | |
| Age at diagnosis | |
| <10 y (A1a) | 26 (49%) |
| >10 y (A1b) | 27 (51%) |
| Disease location (n = 46) | |
| Ileal (L1) | 5 (10.9%) |
| Colonic (L2) | 11 (23.9%) |
| Ileocolonic (L3) | 30 (65.2%) |
| Behavior (n = 44) | |
| Nonstricturing non-penetrating (B1) | 18 (40.9%) |
| Stricturing (B2) | 10 (22.7%) |
| Penetrating (B3) | 10 (22.7%) |
| Stricturing and penetrating (B2B3) | 6 (13.7%) |
| Perianal involvement (n = 48) | 20 (41.7%) |
| Growth retardation (n = 41) | 22 (53.6%) |
| PCDAI score at baseline (range) (n = 35) | 28.7 (5–85) |
| **Biological parameters** | |
| CRP (mg/L) at baseline (range) (n = 49) (N < 5 mg/L) | 25.9 (0–149) |
| Serum albumin (g/L) at baseline (range) (n = 46) (35–50 g/L) | 34.1 (14.4–44.9) |
| ESR (mm) at baseline (range) (n = 43) (N < 15 mm) | 34.5 (3–94) |
| **Treatments** | |
| 5-Aminosalicylic acid (n = 52) | 22 (42.3%) |
| Corticosteroids (n = 53) | 42 (79.2%) |
| Azathioprine (n = 53) | 50 (94.3%) |
| Methotrexate (n = 53) | 21 (39.6%) |
| Anti-TNF-α drugs (n = 53) | 53 (100%) |
| Infliximab | 50 (94.3%) |
| Adalimumab | 41 (77.4%) |
| Other anti-TNF-α | 7 (13.2%) |
| Vedolizumab | 11 (20.7%) |
| Other drugs | 4 (7.5%) |
| Anti-TNF-α adverse event or intolerance | 25 (51%) |
| Psoriasis | 17 (68%) |
| Allergic reaction | 7 (28%) |
| Other | 1 (4%) |

Data are expressed as mean (range), or n (%). BMI = body mass index; CD = Crohn disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PCDAI = Pediatric Crohn Disease Activity Index; TNF-α = tumor necrosis factor alpha; UC = ulcerative colitis.

nausea, headache, infection, and nasopharyngitis. Serious adverse effects were defined as death, a life-threatening condition, a hospitalization (initial or prolonged), a disability or a permanent damage, a congenital anomaly/birth defect, or any other important medical events.

## Statistical Analysis

The results were expressed as mean and range for continuous variables. Categorical variables were expressed as absolute and relative frequencies. The nonparametric Mann-Withney test was used for small samples. The level of statistical significance was set at 5%. All analyses were conducted with the use of GraphPad Prism version 8.00 for Windows (GraphPad Software, La Jolla, CA).

## Ethics Statement

Approval for this study was obtained from the ethic committee of the *Groupe Francophone d'hépatologie, gastroentérologie, nutrition pédiatrique* (approval number 2019-004).

# RESULTS

## Baseline Characteristics

From January 2016 to December 2019, 53 children treated with ustekinumab for IBD were included in this retrospective multicentral study. Forty-eight patients (90.6%) had CD and 5 patients (9.4%) had UC. Thirty-eight patients (72%) were female. The mean age at diagnosis was 9.8 years old (2.3–16). The mean disease duration was 6.7 years (1.1–13.6) and the mean age at ustekinumab induction was 15 years old (8.7–18). The mean and the median duration of follow up were respectively 13 months and 10.5 months (1–51).

Among patients with CD, 30 patients (65%) presented an ileocolonic disease, 11 patients a colonic disease, and 5 patients presented an isolated ileal inflammation. Four patients (7.5%) underwent an endoscopic evaluation at 3 months after treatment induction. All of them presented inflammatory damages and ulcerative lesions. At the last follow-up, 6 patients (11.3%) had an endoscopic evaluation. All of them presented an inflamed mucosa. Twenty-six patients (49%) were diagnosed before 10 years of age (Table 1). Perineal disease was observed in 20 patients (42%). More than half of the patients had a growth delay (54%).

Mean CRP was 25.9 mg/L (0–149). Fifteen patients (30%) had a normal CRP at baseline. Endoscopic evaluation was performed in 39 out of 44 patients; inflammatory damages were found in 37 out of 39 patients and 30 out of 39 presented an ulcerative lesion. Mean PCDAI at baseline was 28.7 (5–85), in 35 patients. At inclusion, 9 patients presented a PCDAI < 15, 20 patients a moderate disease and 6 patients a PCDAI > 45. Of note, 6 patients were in remission (PCDAI < 10). In these patients, ustekinumab was considered due to severe psoriasis in 3 patients, the persistence of



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inflammatory activity during endoscopic evaluation in 2 patients, and the persistence of active fistulas at magnetic resonance enterography in 1 patient.

Prior to ustekinumab induction, all patients had been treated with infliximab, 45 out of 48 (94%) have received azathioprine, 38 out of 48 (79.2%) adalimumab, and 37 out of 48 (77%) corticosteroids (Table 1). Vedolizumab, golimumab, 6-mercaptopurine, certolizumab, and anakinra had also been administered to 11, 5, 3, 2, and 1 patients, respectively. Nine patients (22%) had undergone surgery at ustekinumab induction. Three patients had an ileostomy, 4 patients an ileocecal resection, 1 underwent a colectomy associated with an ileostomy, 1 patient underwent a transverse colostomy, and 1 patient had an ileocecal resection with ileostomy.

Among patients with UC, 4 of them presented pancolitis (E4) and 1 proctosigmoiditis (E2). The mean age at diagnosis was 13 years old (8.9–16). At inclusion, 2 patients presented a mild disease (PUCAI 25 and 35), 2 patients a moderate form (PUCAI 55 in both patients), and 1 patient suffered from a severe colitis (PUCAI 65). The mean PUCAI at ustekinumab induction was 47 (25–65) and mean CRP was 15.8 mg/L (0.5–30). Endoscopic evaluation before starting ustekinumab was performed in all patients. Patients were previously exposed to 5-aminosalicylic acid, corticosteroids, azathioprine, and infliximab. Three patients were treated with adalimumab, 1 patient received golimumab, and 1 patient received vedolizumab.

## Ustekinumab Therapy

In all patients, the initial intravenous (IV) ustekinumab dose was weight-adjusted (6 mg/kg) and the first subcutaneous (SC) dose was 90 mg, 8 weeks after the first dose.

General health indexes and biological parameters significantly improved with ustekinumab. Mean weight significantly increased 3 months after treatment induction, passing from 45 kg (21.5–70.5) to 49 kg (23.3–73) ($P < 0.001$) at baseline (Fig. 1A). Body mass index was significantly higher after 3 months of treatment, 19 kg/m$^2$ (13–32.6) versus 20 kg/m$^2$ (15.7–33.6) ($P < 0.001$) (Fig. 1B). Statistical analysis showed a significant decrease of CRP levels at 3 months ($P < 0.05$) and at the last follow-up ($P < 0.001$) compared to baseline (Fig. 1C). Blood albumin level was significantly higher at 3 months ($P< 0.005$) and at the last follow-up ($P < 0.001$) (Fig. 1D). In addition, ESR was significantly lower at the last follow-up ($P< 0.001$) compared to baseline (Fig. 1E) and hematocrit rate was significantly higher at the last follow-up ($P < 0.005$) (Fig. 1F). Fecal calprotectin levels are shown in Figure 1G.

PCDAI and PUCAI improved with ustekinumab treatment. PCDAI score significantly decreased at 3 months compared to baseline (Fig. 2A) ($P < 0.05$). Seventeen patients (48%) presented a PCDAI < 15 at 3 months of therapy. At the last follow-up, 20 patients (57%) had a PCDAI < 15 (Fig. 2A). For UC patients, PUCAI showed a significant improvement, 25 (15–40) at 3 months and 18.3 (0–35) at the last follow-up, compared to 47 (25–65) at the baseline (Fig. 2B). At 3 months, CRP was normalized in 75% of patients.

Nine patients (16%) were steroid-free at inclusion, 31 (58%) at 3 months, and 33 (62%) at the last follow-up.

During the 13 months of follow-up, 9 patients had adverse effects. The more frequent ones were fatigue in 3 patients (3%) and headache in 3 patients (3%). One patient had recurrent respiratory tract infections, resulting in ustekinumab discontinuation.

Ustekinumab treatment was discontinued in 15 patients (28%) due to a lack of efficiency in 8 patients (53%), loss of response in 5 patients (33%), and exacerbation of an associated chronic recurrent multifocal osteomyelitis in 1 patient (6.7%). The treatment was discontinued in the first 3 months in 7 patients (46.6%) and after 3 months in 8 patients (53.4%). Twenty-four patients benefited from an optimized therapy, 1 injection every 4 weeks, at 3 months.

## Perianal Crohn Disease (pCD)

Twenty patients (42%) suffered from an active or inactive perineal disease. Nine patients presented an active perineal lesion at the induction of ustekinumab therapy. One patient developed a perineal inflammation with ustekinumab therapy. Five patients (50%) showed improvement of the lesions under treatment with ustekinumab. Among 20 patients, the mean PCDAI was 25.6 (5–55) in pCD patients compared to 30.8 (5–85) in non-pCD patients ($P = 0.432$) at induction (Fig. 3A). After 3 months of treatment, mean PCDAI was 22.5 (2.5–75) in pCD patients compared to 14.3 (0–37.5) in non-pCD patients ($P = 0.17$). At the last follow-up, mean PCDAI was 19 (0–60) in pCD patients compared to 8.5 (0–35) in non-pCD patients ($P = 0.04$). The mean CRP at inclusion, 3 months, and at last follow-up was identical between the 2 groups (Fig. 3B).

# DISCUSSION

This multicentral study from 9 French tertiary care centers of the GETAID pédiatrique included both CD and UC patients and provided real-life data which characterized and evaluated the short- and long-term effectiveness of ustekinumab therapy in pediatric IBD. Our results confirmed that ustekinumab is a well-tolerated therapy after anti-TNF-α failure or loss of tolerance. No serious adverse effects were reported and only 1 patient stopped the treatment because of recurrent respiratory tract infections.

In our cohort, as in adult studies, ustekinumab was used in case of resistance or intolerance to anti-TNF-α therapy (Table 1). Even though ustekinumab has already demonstrated clinical efficacy in the induction and the maintenance of remission in adult refractory patients (16–18), the data in pediatric IBD is scarce. Few multicenter retrospective studies have showed an effective response to ustekinumab therapy, approaching 50% (19,20). Chavannes et al (21), in a multicenter retrospective study of 44 pediatric patients, reported clinical remission in 38.6% of the patients and clinical response in 47.8%, at 12 months. Recently, the UniStar study, a prospective multicenter study, randomized 44 children in 2 groups, a lower induction (3 mg/kg) ustekinumab dose and a higher induction (9 mg/kg) group (22). At week 8, 48% of patients from both groups showed a favorable clinical response. Moreover, at week 16, 30% of the patients treated with a higher induction dose (9 mg/kg), presented clinical remission with a PCDAI < 10. In our study, the clinical response after 3 months of therapy was 48% for CD patients. This result is concordant with the previous studies. Interestingly, Dayan et al reported 10 bio-naïve patients whom presented a higher rate of response with 90% in steroid-free remission at week 52, suggesting a higher efficiency of ustekinumab in patients naïve of biotherapy.

Clinical characteristics and biological inflammation were positively impacted by ustekinumab therapy in our study. Indeed, patients significantly improved their weight, body mass index, and albumin and significantly decreased their CRP levels. This was consistent with a GETAID retrospective adult study reporting a decrease in CRP in 95% of patients 3 months after ustekinumab induction (23), as well as in the UniStar study showing a decrease in CRP and fecal calprotectin at week 8 and 16 (22). Contradictory, Chavannes et al, the UNITI-1/2, and IM-UNITI trials reported higher CRP levels at 3- and 12-months follow-up in treated patients (18,21). Overall, CRP does not seem to be a reliable biomarker for disease response to ustekinumab therapy. Unfortunately,



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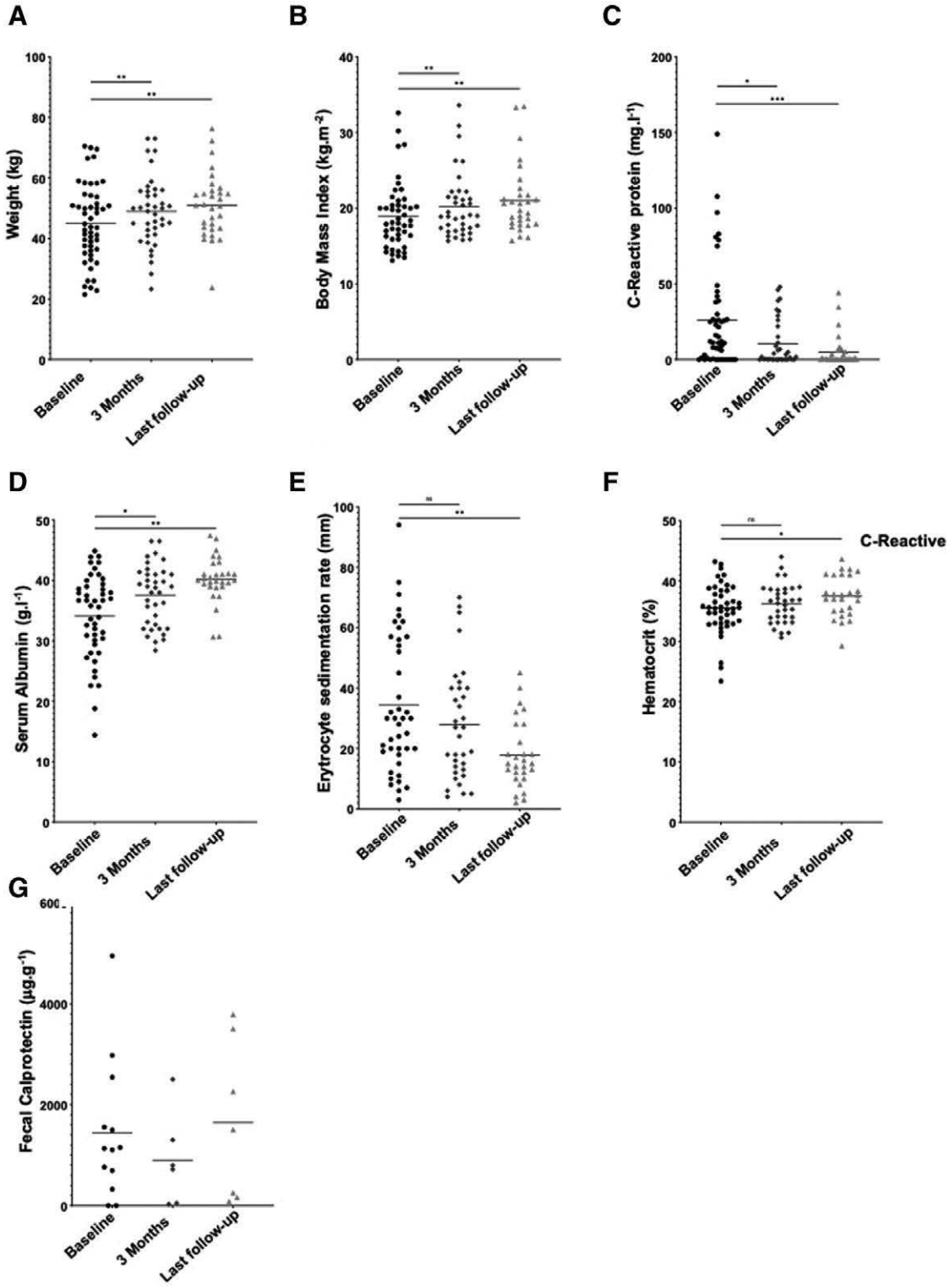


**FIGURE 1.** Anthropometric and biological parameters at baseline, 3-month after induction, and at the last follow-up. (A) Weight; (B) body mass index; (C) C-reactive protein; (D) serum albumin; (E) erythrocyte sedimentation rate; (F) hematocrit; (G) fecal calprotectin.



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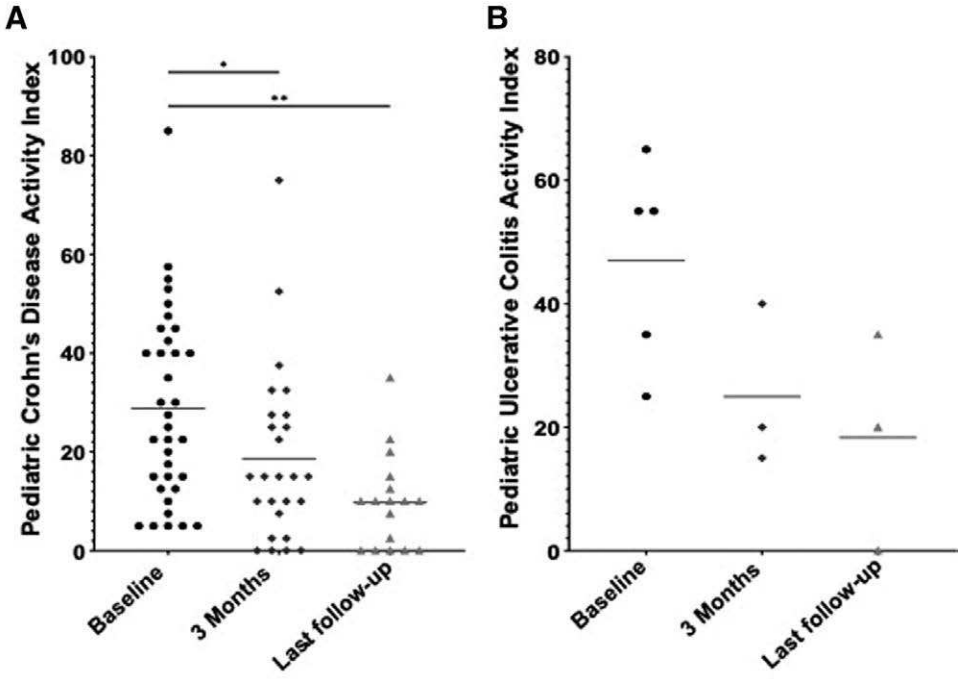


**FIGURE 2.** Disease activity scores at baseline, 3-month after induction, and at the last follow-up. (A) Pediatric Crohn Disease Activity Index; (B) Pediatric Ulcerative Colitis Activity Index.

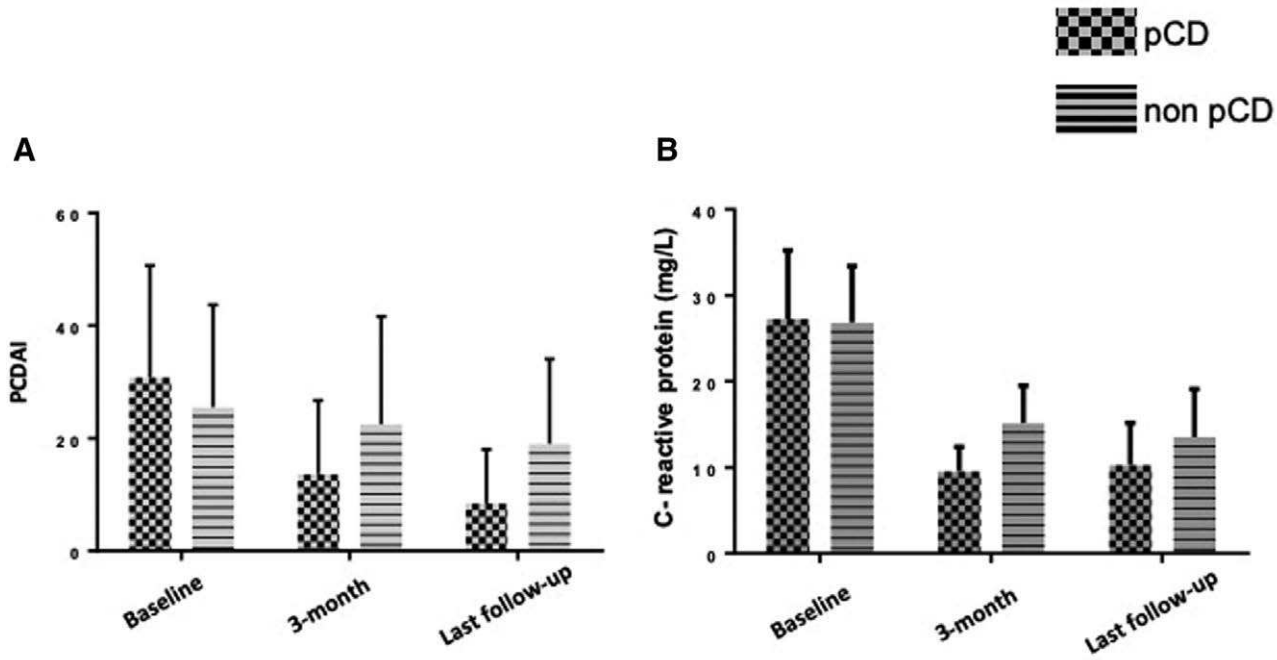


**FIGURE 3.** Comparison between patients with perianal disease (pCD) versus patients without perianal disease (non-pCD) at baseline, 3-month after induction, and at the last follow-up. (A) Pediatric Crohn Disease Activity Index; (B) C-reactive protein. pCD = perianal Crohn disease.



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calprotectin fecal samples were missing to determine the response to ustekinumab therapy.

Induction regimen of ustekinumab could be different between studies. Wils et al (23) for example reported 13 different induction regimens from 20 French centers. After 3 months, any significant association was found between induction regimen and clinical outcome. Interestingly, Chavannes et al showed that a higher induction dose was associated with lower discontinuation rates arguing that the weighted based IV induction regimen may be more effective by avoiding an underdosed therapy. In our study, the induction regimen was similar in all patients with a dose weighted IV induction at 6 mg/kg followed by a SC injection at 90 mg.

In our study, treatment was discontinued in 28% of patients. These results are similar to retrospective studies in children which reported a 30% of discontinued medication as well as studies reported in adult populations (21,24–27). Interestingly, the UniStar study reported discontinued therapy in only 2 patients.

In our study, no patients faced a severe adverse event, in accordance with former adult and pediatric studies. Fatigue and headache were the most common side effects observed in 7% of patients, much lower than the 16% of patients suffering from headaches in UniStar pediatric study. As already described, we reported 2 cases (4.7%) of infections which was much lower than in the UniStar study (39%) and in accordance with CERTIFI study which reported 5.6% of nasopharyngitis. Of importance, no severe infections were reported either in our study or in the UniStar study (22). Overall, ustekinumab could be considered as a safe therapy for children. Although long-term safety data for ustekinumab is limited in IBD, extrapolation from Psoriasis Longitudinal Assessment and Registry suggests no increased risk of serious infection, malignancy, or mortality (28).

The efficiency of ustekinumab in pCD is poorly known. Interestingly, 9 patients presented an active perineal lesion at the treatment induction in our study. Five patients improved their perineal disease with ustekinumab therapy. A French retrospective adult study, BIO-Lap, estimated that 37.8% of patients receiving ustekinumab during an active perineal disease reached clinical success and did not require further medical or surgical interventions for perianal lesions at 6 months (29). Furthermore, a pooled study of patients with an active fistula at inclusion in both CERTIFI, UNITI-1/UNITI-2 showed insignificant but higher rates of fistula closure after 8 weeks of treatment for 161 (24.7%) patients in the ustekinumab group compared with the 77 (14.1%) patients in the placebo group (30). Overall, those studies suggested an encouraging role of ustekinumab in the treatment of pCD but further studies are necessary.

In adult patients, ustekinumab is used as therapy for UC patients resistant to anti-TNF-α and has recently been validated as a therapeutic option in a multicenter randomized double blind versus placebo study showing 15% of remission at week 8 (10). Moreover, Dayan et al reported 10 patients who benefited of ustekinumab therapy and showed 60% of clinical remission at week 52. In our cohort, 5 patients with UC were treated with ustekinumab. All of them had received vedolizumab before. They all showed decrease in disease activity and overall improvement. Even though more data is needed in order to evaluate the efficiency of ustekinumab in resistant UC.

Yet, our study has several limitations, among them the retrospective design, the lack of PCDAI in few patients, and the evaluation of fecal calprotectin and endoscopic score. While our study provides new data for UC patients, these appear to be limited due to the small number of patients included and need to be confirmed. However, through clinical and biological features, we displayed that ustekinumab had a significant positive impact in more than 50% of our patients which was in total accordance with the literature.

## CONCLUSIONS

In conclusion, ustekinumab seems to be effective in achieving and maintaining remission in pediatric patients with anti-TNF-α refractory IBD. Clinical activity scores, biochemical parameters of disease activity, and growth parameters have been improved. The tolerance profile was excellent, and no serious adverse events were observed throughout the follow-up.

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