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Upadacitinib for Induction of Remission in Paediatric Crohn's Disease: An International Multicentre Retrospective Study

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ABSTRACT

Background: There are scarce data available on upadacitinib in children with Crohn's disease (CD).

Aim: To evaluate the effectiveness and safety of upadacitinib as an induction therapy in paediatric CD.

Methods: This was a multicentre retrospective study between 2022 and 2024 of children treated with upadacitinib for induction of remission of active CD conducted in 30 centres worldwide affiliated with the IBD Interest and Porto group of the ESPGHAN. We recorded demographic, clinical and laboratory data and adverse events (AEs) at week 8 post-induction. The analysis of the primary outcome was based upon the intention-to-treat (ITT) principle.

Results: We included 100 children (median age 15.8 [interquartile range 14.3–17.2]). All were previously treated with biologic therapies including 89 with ≥2 biologics. At the end of the 8-week induction period, we observed clinical response, clinical remission and corticosteroid- and exclusive enteral nutrition-free clinical remission (CFR) in 75%, 56% and 52%, respectively. By the end of induction, 68% had achieved normalisation of C-reactive protein, and 58% had faecal calprotectin (FC) <150 mcg/g. There was combined CFR and FC remission in 13/31 children with available data at 8 weeks (13% of the ITT population). AEs were recorded in 24 children; the most frequent was acne in 12. Two AEs (severe acne and hypertriglyceridemia) led to discontinuation of therapy.

Conclusion: Upadacitinib is an effective induction therapy for refractory paediatric CD. Efficacy should be weighed against the potential risks of AEs.

For affiliations refer to page 1379.

1 | Introduction

Current guidelines recommend anti-tutor necrosis factor-alpha (TNFα) agents in children with active Crohn's disease (CD) who fail to achieve or maintain remission with steroids or exclusive enteral nutrition (EEN) and an immunomodulator or who are at high risk for a complicated disease course [1]. Real-world data support the use of other biologics, such as vedolizumab and ustekinumab and Janus kinase (JAK) inhibitors such as tofacitinib, that are approved for adults but not yet for children with refractory disease [2–4]. Upadacitinib, a selective JAK1 inhibitor, has demonstrated superiority over placebo in both induction and maintenance phase 3 studies for clinical, endoscopic and histologic endpoints in adult populations with UC [5–7] and CD [8, 9]. Upadacitinib studies revealed a relatively high efficacy in patients who were refractory to advanced therapies [5–9].

While upadacitinib has not been approved for paediatric inflammatory bowel disease (IBD), it is used off-label in children with refractory disease. Efficacy data in paediatric IBD are limited to a single centre retrospective case series of 20 adolescents, of whom 15 achieved corticosteroid-free clinical remission at week 12 of therapy with no new safety signals [10]. Dual advanced therapy, which comprises a combination of two biologics or a biologic with JAK inhibitor, is increasingly recognised as a potential therapeutic option of refractory IBD [11, 12]. In their paediatric series, Spencer et al. reported all 7 adolescent patients under combined upadacitinib and ustekinumab therapy achieved remission following induction [10]. Safety data for upadacitinib in the paediatric population are derived mostly from studies on atopic dermatitis [13], where upadacitinib therapy is approved for children > 12 years and has been investigated for children aged > 2 years [14, 15]. Notably, the recommended initial daily dose for atopic dermatitis is 15 mg, compared to the higher 45 mg daily dose recommended for IBD in adults [13–15].

The aim of this study was to evaluate effectiveness, safety and dosing of upadacitinib for the induction of remission in paediatric CD.

2 | Methods

2.1 | Study Design and Patient Population

This was a retrospective cohort study from 30 centres in Europe and the Middle East, affiliated with the Paediatric IBD Interest and Porto group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), as well as centres in North America (including patients from the Mt. Sinai cohort [10]). Included were children and adolescents (≤ 18 years of age) diagnosed with CD according to the revised Porto criteria [16], who were treated with upadacitinib for the induction of remission of active disease between January 2022 and March 2024, and had a follow-up of at least 8 weeks. Active disease was defined as weighted Paediatric Crohn's Disease Activity Index (wPCDAI) ≥ 12.5 [17]. To allow for intention-to-treat (ITT) analyses and avoid selection bias, we included all patients who received an upadacitinib dose. Children that discontinued therapy were considered treatment failures.

2.2 | Data Collection

Patient demographic and clinical characteristics were collected. Disease characteristics were documented according to the Paris classification [18], and disease activity was measured by the wPCDAI [17]. Past and concomitant therapy, surgeries and laboratory results were documented at the initiation of upadacitinib therapy and during 8 weeks of follow-up. Data at 4 weeks of follow-up (±1 week) were also collected, when available. All adverse events (AEs) that were potentially related to therapy according to the judgement of the treating physician were recorded. Serious AEs were defined as those that were life-threatening or resulted in hospitalisation, disability or discontinuation of therapy.

2.3 | Outcomes

The primary outcome of the study was corticosteroid- and EEN-free clinical remission (CFR) at the end of the 8-week induction period of upadacitinib therapy. Secondary outcomes included clinical remission, clinical response, normalisation of C-reactive protein (CRP), decrease of faecal calprotectin (FC) to < 150 mcg/g, combined CFR and FC remission (CFR and decrease of FC to < 150 mcg/g), need for IBD-related surgery during follow-up, durability of therapy and AEs.

Clinical remission was defined as a wPCDAI < 12.5, clinical response as a wPCDAI reduction of > 20 points, and normalisation of CRP as a level < 5 mg/L. Hyperlipidaemia was defined according to the recommendations of the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Serum low-density lipoprotein cholesterol ≥ 130 mg/dL or total cholesterol ≥ 200 mg/dL or triglycerides ≥ 100 mg/dL at 0–9 years or ≥ 130 mg/dL above 10 years of age [19].

2.4 | Statistical Analysis

Continuous variables were expressed as median and interquartile range [IQR]. Categorical variables were presented as frequency and percentage. Categorical variables were compared by Chi-squared test or the Fisher exact test, as appropriate, while continuous variables were compared with the Mann–Whitney test. A generalised estimating equations model was applied for repeated measures analysis. The analyses of the primary outcome were performed under the ITT principal. Data of clinical outcomes at Week 8 were available for all patients unless therapy had been discontinued earlier. In case of early discontinuation, patients were considered as treatment failures. Imputation to missing laboratory data was not performed; the number of patients with available data for each determinant were detailed in the appropriate tables. All the statistical tests were 2-tailed. A $p < 0.05$ was considered statistically significant. SPSS (version 27; IBM Corporation) was used for all statistical analyses.

2.5 | Ethical Considerations

This study was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center (TLV-23-0723) and equivalent

committees of the contributing centres. Informed consent was waived as this was an anonymised retrospective study.

3 | Results

A total of 100 children were included in the study. Their median (IQR) age was 15.8 (14.3–17.2) years (range 9–18 years) at the initiation of upadacitinib therapy (Table 1), and their median (IQR) disease duration was 4.4 (2.3–6.7) years. Before receiving upadacitinib therapy, all children had been treated with biologic agents: 97 with anti-TNFα agents (33 with infliximab, 20 with adalimumab, 44 with both agents), 83 with ustekinumab, 31 with vedolizumab, and 5 with risankizumab (Table 1). Eleven patients were treated with tofacitinib. All patients had an active CD at the initiation of upadacitinib therapy.

3.1 | Upadacitinib Dosing and Combination Therapies

The induction doses of upadacitinib are presented in Table 2. Eighty-six (86%) patients received an induction dose of 45 mg/day, while the others received lower doses as presented in Table 2. The median daily dose of children weighing 30–40 kg was 1.2 (0.9–1.3) mg/kg or 35.8 (27.1–36.9) mg/m^2 body surface area (BSA) and for those weighing 20–30 kg it was 1.3 (1.3–1.6) mg/kg or 33.2 (31.5–42.4) mg/m^2 BSA (Table 2).

Upadacitinib was provided at baseline as combination therapy in 47 children as follows: biologic agents ($n=22$: 17 ustekinumab, 3 risankizumab, 2 vedolizumab), corticosteroids ($n=21$), EEN ($n=4$), 5-aminosalicylic acid (5-ASA) ($n=2$) and azathioprine ($n=1$). In all cases of combination of upadacitinib with steroids or biologic agent, upadacitinib therapy was added to ongoing steroid or biologic therapy.

3.2 | Study Outcomes

At the end of the induction period, 89 (89%) children were still receiving upadacitinib therapy. The shortest exposure time was 4 weeks in one patient. Eight of the 11 children who discontinued therapy did so due to non-response. One child discontinued therapy due to non-response and elevated serum triglycerides, one child due to acne, and one child due to the patient's preference. Two children underwent surgeries after 8 weeks of therapy (one ileocecal resection who discontinued therapy and one diverting ileostomy). Clinical response, clinical remission and CFR at week 8 were observed in 75 (75%), 56 (56%) and 52 (52%) children, respectively. The median wPCDAI decreased from 30 (18–54) to 8 (0–19) at week 8 ($p<0.001$) (Table 3, Figure 1A). Thirteen of the 21 children (62%) treated with corticosteroids at the initiation of upadacitinib therapy were steroid-free by week 8. Among the 22 children treated with upadacitinib in combination with a biologic agent, 7 discontinued the biologic agent (5 ustekinumab and 2 risankizumab) during the induction period.

At baseline, 58/99 (59%) patients had elevated CRP levels and 41/48 (85%) patients had FC > 150 mcg/g levels. CRP levels were available for 77 children and FC levels were available for 31 children at week 8. Fifty-two (68%) children had normal CRP levels post-induction [38/58 (66%) of the patients with elevated CRP at baseline]. Eighteen (58%) children had FC levels < 150 mcg/g post-induction [14/31 (45%) of the patients with available data and elevated FC at baseline]. The median FC level declined from 800 (327–2100) at baseline to 98 (20–1170) mcg/g at week 8 ($p=0.011$) (Table 3, Figure 1B). Combined CFR and FC remission was observed in 13/31 (42%) children whose data were available. The longitudinal changes in laboratory measures are presented in Table 3. Among the study cohort, 24% of the children had perianal involvement. Among these 24 children, 6 children had an active perianal disease at the initiation of upadacitinib therapy. Of these 6 children, 3 achieved complete remission of their perianal disease after induction.

Data at 4 weeks of follow-up were available for 66 patients. Clinical response, clinical remission and CFR were reported for 29 (44%), 22 (33%) and 16 (24%) patients, respectively, with available data (29%, 22% and 16% of the ITT population).

3.3 | Predictors of Outcomes

While the daily dose per BSA was higher among children weighing < 40 kg, this value was not associated with the primary outcome [a CFR in 9/18 (50%) patients below 40 kg vs. 43/82 (52%) patients above 40 kg, $p=0.851$]. The clinical response at 4 weeks was a predictor to CFR at week 8 [odds ratio = 26 (95% confidence interval 5–139), $p<0.001$]. In a multivariate analysis that included week 4 clinical response and wPCDAI at the initiation of upadacitinib therapy, week 4 clinical response was an independent predictor of week 8 CFR (odds ratio = 24, 95% confidence interval 4–136, $p<0.001$). A further analysis that included also age and sex revealed similar results (odds ratio = 35, 95% confidence interval 5–247, $p<0.001$). Overall, 21/29 (72%) patients who had responded to therapy at 4 weeks of follow-up achieved CFR at week 8. Among 37 children who have not experienced clinical response at week 4, only 2 (5%) patients achieved CFR by week 8. No therapy change was conducted in these 2 children. However, both of them did not exhibit severe disease at the initiation of upadacitinib therapy (wPCDAI of 42.5 and 22.5 points). Additional week 4 clinical and laboratory variables that were associated with CFR at week 8 are presented in Table S1. None of the baseline variables, such as age, sex, disease duration and phenotype, extra-intestinal manifestations, past therapies, dosing regimen and combination therapy were associated with the clinical outcomes. The rates of CFR were comparable between patients under dual advanced therapy (upadacitinib and biologic agent) and patients under upadacitinib monotherapy (Table 1).

3.4 | Adverse Events

AEs that were potentially related to upadacitinib therapy were reported for 24 children (Table 4). The most frequent AE was acne ($n=12$). The two AEs that led to discontinuation of upadacitinib were severe acne and elevated serum triglycerides (233 mg/dL). The baseline and follow-up lipid status data of the patients are presented in Table S2. One of the two patients who sustained infectious AEs was treated with a combination

TABLE 1 | Demographic and clinical data of the study cohort.

	All cohort ($n = 100$)	Absence of CFR at week 8 ($n = 48$)	CFR at week 8 ($n = 52$)	p
Age at diagnosis of CD, years	10.7 (8.4–12.6)	10.1 (8.3–12.8)	11.1 (8.2–12.6)	0.579
Age at upadacitinib therapy, years	15.8 (14.3–17.2)	16.3 (14.6–17.4)	15.7 (13.9–17.0)	0.168
Duration of CD, years	4.4 (2.3–6.7)	5.5 (2.3–7.8)	3.9 (2.1–5.9)	0.109
Males	59 (59%)	24 (50%)	35 (67.3%)	0.079
Location of CD:				0.227
Ileo-caecal	15 (15%)	7 (14.6%)	8 (15.7%)	
Colonic	17 (17%)	5 (10.4%)	12 (23.5%)	
Ileo-colonic	66 (66%)	35 (72.9%)	31 (60.8%)	
Upper GI only	1 (1%)	1 (2.1%)	0	
Upper GI involvement	34 (34%)	17 (35.4%)	17 (32.7%)	0.774
CD behaviour:				0.657
Inflammatory	83 (83%)	41 (85.4%)	42 (80.8%)	
Stricturing	9 (9%)	4 (8.3%)	5 (9.6%)	
Penetrating	6 (6%)	2 (4.2%)	4 (7.7%)	
Stricturing and penetrating	2 (2%)	1 (2.1%)	1 (1.9%)	
Perianal involvement	24 (24%)	14 (29.2%)	10 (19.2%)	0.245
Growth impairment	35 (35%)	17 (35.4%)	18 (34.6%)	0.933
Extraintestinal manifestations	26 (26%)	16 (33.3%)	10 (19.2%)	0.108
Previous therapy:				
Corticosteroids ($n = 58$)	43 (74.1%)	18 (75%)	25 (73.5%)	0.900
5-ASA ($n = 58$)	19 (32.8%)	9 (37.5%)	10 (29.4%)	0.518
Thiopurines	31 (31%)	12 (25%)	19 (36.5%)	0.213
Methotrexate	19 (19%)	9 (18.8%)	10 (19.2%)	0.951
Infliximab	77 (77%)	40 (83.3%)	37 (71.2%)	0.148
Adalimumab	64 (64%)	32 (66.7%)	32 (61.5%)	0.594
Vedolizumab	31 (31%)	18 (37.5%)	13 (25%)	0.177
Ustekinumab	83 (83%)	41 (85.4%)	42 (80.8%)	0.536
Risankizumab	5 (5%)	4 (8.3%)	1 (1.9%)	0.192
Tofacitinib	11 (11%)	8 (16.7%)	3 (5.8%)	0.082
Thalidomide	3 (3%)	2 (4.2%)	1 (1.9%)	0.606
Tacrolimus	3 (3%)	2 (4.2%)	1 (1.9%)	0.606
Surgery	9 (9%)	5 (20.8%)	4 (11.8%)	0.347
Dual advanced therapy ($n = 58$)	10 (17.2%)	3 (12.5%)	7 (20.6%)	0.422
Number of failed biologics				0.059

(Continues)

TABLE 1 | (Continued)

	All cohort ($n=100$)	Absence of CFR at week 8 ($n=48$)	CFR at week 8 ($n=52$)	p
1	11 (11%)	2 (4.2%)	9 (17.3%)	
2	39 (39%)	17 (35.4%)	22 (42.3%)	
3	33 (33%)	21 (43.8%)	12 (23.1%)	
4	17 (17%)	8 (16.7%)	9 (17.3%)	
wPCDAI at baseline	30 (18–54)	36.3 (20–57.5)	26.3 (15–43.8)	0.065
Simple Endoscopic Score-CD at baseline	12 (6–19)	14 (9–21)	11 (3–15)	0.101
Corticosteroids at baseline	21 (21%)	12 (25%)	9 (17.3%)	0.345
Biologics at baseline	22 (22%)	14 (29.2%)	8 (15.4%)	0.096

Note: Data are presented as median (interquartile range) for continuous variables and number (%) for categorical variables.
Abbreviations: 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; CFR, corticosteroid-free clinical remission; GI, gastrointestinal; wPCDAI, weighted paediatric Crohn's disease activity index.

TABLE 2 | Induction doses of upadacitinib.

Daily dose	All cohort ($n=100$)	Weight 30–40 kg ($n=13$)	Weight 20–30 kg ($n=5$)
45 mg	86 (86%)	9 (69%)	2 (40%)
30 mg	12 (12%)	4 (31%)	3 (60%)
15 mg	2 (2%)	0	0
Dose in mg/m^2 BSA[a]		35.8 (27.1–36.9)	33.2 (31.5–42.4)
Dose in mg/kg[a]		1.2 (0.9–1.3)	1.3 (1.3–1.6)

Abbreviation: BSA, body surface area.
[a]Data are presented as median (interquartile range).

of steroids and upadacitinib. There were no thromboembolic events, severe infections or malignancies. None of the patients were given *Pneumocystis jirovecii* pneumonia prophylaxis.

4 | Discussion

This is the first multicentre analysis of children with refractory CD treated with upadacitinib for the induction of remission. CFR and combined CFR and FC remission were demonstrated by week 8 in 52% and 42% of the children, respectively.

The rates of clinical remission with upadacitinib daily dose of 45 mg in two phase 3 induction trials among adults were 50% and 39% [8]. Steroid-free remission was reported for 43% and 34%, and clinical response was reported for 57% and 51% of the patients [8]. A prospective analysis of 105 adults with IBD (40 with CD) who were treated with upadacitinib reported that 71% of the CD patients achieved clinical remission and 77% achieved response at 8 weeks [20]. A comparable rate of 64% for clinical remission was reported in a retrospective study on 93 adults with CD [21]. A smaller retrospective study ($n=33$) reported lower rates for clinical response (64%) and remission (27%) [22]. Meta-analyses of clinical studies on upadacitinib in the treatment of IBD reported clinical remission rates of 25%–55% and clinical response rates of 42%–65%, with corresponding rates of 46% and 54% in a CD population [23]. The clinical response rate for upadacitinib 45 mg daily dose was highest in a network metaanalysis that included 25 studies on advanced therapies in bio-exposed patients with CD [24]. Improvements in health-related quality of life were also achieved and sustained with upadacitinib-treated patients with moderate-to-severe CD [25]. Taken together, the main clinical endpoints in our current paediatric study (clinical response of 75%, clinical remission of 56% and CFR of 52% at week 8) are comparable to those in the real-life adult population. The only previously published paediatric case series on upadacitinib therapy in IBD reported steroid-free remission 4/9 (44%) patients with CD post-induction [10].

The phenotype of CD was not associated with the outcomes of therapy in our paediatric cohort. This conclusion is limited by the small sample size and the predominance of ileocolonic involvement in our cohort. Studies in adults have reported higher rate of clinical remission in patients who had no small intestinal involvement compared to patients who did [21, 22], similarly to Spencer et al. [10] that reported that all 3 of their paediatric patients with colonic CD achieved steroid-free remission post-induction compared to 1/6 (17%) with ileocolonic CD. Upadacitinib has also been reported to be effective in managing perianal fistulizing CD [26].

The vast majority of the patients in our cohort (86/100, 86%) received an upadacitinib induction dose of 45 mg daily. In addition,

TABLE 3 | Clinical and laboratory measures during follow-up.

	Baseline	Follow-up at 4 weeks	Follow-up at 8 weeks	*p*
wPCDAI	30 (18–54) *n* = 100	10 (0–18) *n* = 66	8 (0–19) *n* = 100	**< 0.001**
Haemoglobin (g/dL)	11.8 (10.6–13) *n* = 99	12.8 (12–14.4) *n* = 33	12.1 (11.6–12.9) *n* = 76	**0.035**
CRP (mg/L)	12.7 (5.5–26.5) *n* = 99	0.7 (10–11.5) *n* = 33	3.4 (0–17.4) *n* = 77	**0.034**
ESR (mm/h)	40 (24–55) *n* = 94	3 (2–14) *n* = 30	19 (5–27) *n* = 67	**< 0.001**
Albumin (g/L)	37 (33–41) *n* = 99	44 (42–45) *n* = 30	42 (39–44) *n* = 75	**< 0.001**
Faecal calprotectin (mcg/g)	800 (327–2100) *n* = 48	470 (18–2769) *n* = 15	98 (20–1170) *n* = 31	**0.011**

Note: Data are presented as median (interquartile range). Bold denotes significant.
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; wPCDAI, weighted paediatric Crohn's disease activity index.

39% of those who weighed < 40 kg and 60% of those who weighed < 30 kg received reduced dosage, however, their dose for BSA or weight was higher compared to patients who weighed > 40 kg. Nevertheless, the dosing regimen was not associated with clinical outcomes. The association between dosing, plasma exposure and efficacy of upadacitinib has been established in adults, with a dose of 45 mg having been shown to maximise efficacy for induction [27]. Twenty-two children in our study were treated with combinations of upadacitinib and another advanced therapy, and no difference in clinical outcomes was observed between them and the children who were treated with upadacitinib as monotherapy. In their paediatric cohort, Spencer et al. [10] reported that all 7 adolescent patients under combined upadacitinib and ustekinumab therapy achieved remission following induction. All 10 adult patients with CD that were treated by Miyatani et al. with the combination of upadacitinib and ustekinumab achieved clinical response and 5/6 achieved remission [28]. Importantly, while combining advanced therapies may have potential efficacy, their use should be weighed against the risks of serious adverse events [11, 12].

Steroids at baseline have also been associated with CFR in all 6 adults treated with that combination [20]. Peyrin-Biroulet et al. evaluated the effect of prior therapy for CD and reported that upadacitinib led to higher rates of favourable clinical and endoscopic outcomes in patients who were naïve to biologic therapy [29]. Although limited by the low number of tofacitinib-experienced patients, our study findings showed no difference in the response or remission rates between tofacitinib-naïve and tofacitinib-experienced children, comparable to the results observed in paediatric and adult studies [10, 20]. These data may support the beneficial use of upadacitinib in patients who have been previously exposed to tofacitinib. The effectiveness of upadacitinib compared to previous studies of tofacitinib should be interpreted with caution, due to difference in populations, study designs and interpretation of the results.

The respective rates of clinical response, clinical remission and CFR were 44%, 33% and 24% after 4 weeks of therapy among our paediatric patients. These data are supported by studies

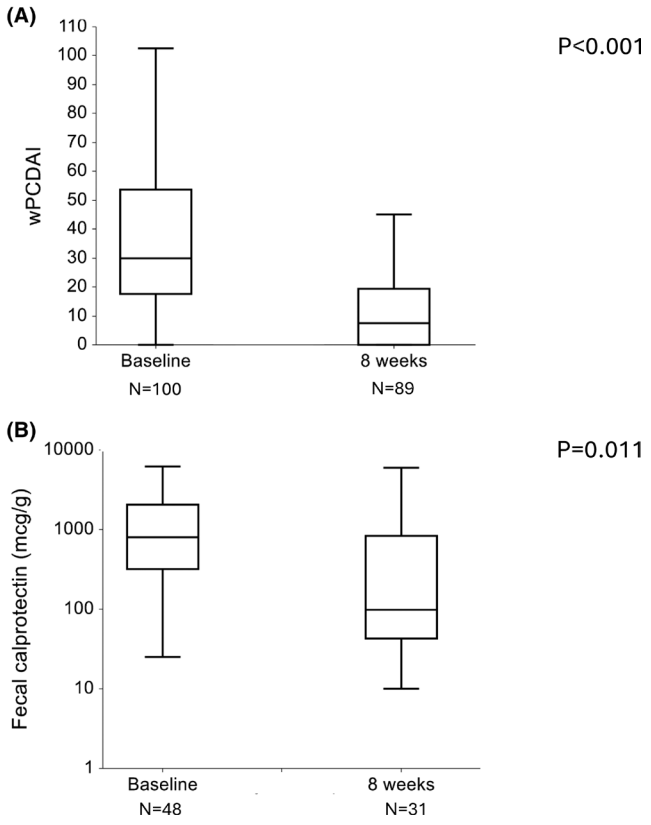

FIGURE 1 | (A) wPCDAI at baseline and at week 8. (B) Faecal calprotectin at baseline and at week 8.

that reported improvement in symptoms as early as week 2 in adult populations [8, 20]. The authors of a post hoc analysis of data from two phase 3 induction trials and 1 maintenance trial (*n* = 1021 patients) observed improvement of symptoms after a median of 13 days [30]. Improvement in fatigue and quality of life were observed as early as week 4 [31]. The rapid onset of response makes upadacitinib therapy particularly promising for patients with severe or steroid-dependent CD by facilitating rapid withdrawal from steroids. Our study findings support the association between week 4 clinical response and improvement

TABLE 4 | Adverse events.

	Number of patients
Serious adverse events	
Hypertriglyceridemia	1
Acne	1
Other adverse events	
Acne	12
Hyperlipidaemia	4
Headache	3
Infections	
Herpes simplex	1
Adenovirus hepatitis and upper respiratory tract	1
Lymphopenia	1
Elevated serum aminotransferases	1
Transient increase in serum lipase	1
Worsening of alopecia	1

in inflammatory markers to remission by the end of week 8. Twenty-one of our 29 (72%) patients who had already responded to therapy at 4 weeks achieved CFR by week 8. Our finding that only two of 37 children who have not experienced clinical response at week 4 achieved CFR by week 8 emphasises the importance of early monitoring.

Consistent with clinical outcomes, improvements in CRP and FC post-induction were reported in paediatric and adult patients treated with upadacitinib [10, 20–22, 32, 33]. The rates of normal CRP values (68%) and FC < 150 mcg/g (58%) at week 8 in our paediatric study were high, and the decline in FC from a median of 800 at baseline to less than 100 mcg/g was also significant.

The most frequent AE in our study was acne, which could be considered as a major concern, particularly in paediatric and adolescent population. No thromboembolic events, serious infections or malignancies were reported. Upadacitinib was discontinued in one patient with severe acne and in one patient with elevated serum triglycerides. In the phase 3 induction studies on adults, serious AEs were reported in 7%–9% of the patients, with low rates of treatment discontinuation due to AEs [8]. In their prospective study, Freidberg et al. also reported that the most common AE was acne, occurring in 23% of their adult patients [20]. Notably, a meta-analysis showed no difference in the rate of AEs in patients that were treated with upadacitinib compared to placebo [23]. Nevertheless, the warning by the European Medicines Agency regarding the increased risk of venous thromboembolism, cancer and major cardiovascular conditions mandates careful consideration [34].

This is the first and largest multicentre study on a cohort of children with CD treated with upadacitinib. However, the study is limited by its retrospective nature, which prevented a structured follow-up of data, and specifically lacked an organised reporting of week 4 outcomes, missing laboratory data, and a systematic monitoring AEs. Another limitation is the absence of endoscopic follow-up data, since this endpoint was available for only a small subset of patients during induction. Due to the limited number of patients, a multivariate analysis was not feasible for all the studied outcomes. The study is also limited by the small number of young children included. An additional limitation is the short-term follow-up and the clear need of long-term data on the efficacy and safety of upadacitinib in children.

In conclusion, the findings of this study suggest that upadacitinib therapy is effective for induction of remission in children with refractory CD, improving clinical and biomarker outcomes. The data support the beneficial use of upadacitinib in children who have previously failed tofacitinib. While the safety profile was generally favourable, the efficacy of upadacitinib should be weighed against the potential risk of AEs.

Author Contributions

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Conflicts of Interest

Last 3 years D.T. received consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Shaare Zedek Medical Center, Hospital for Sick Children, Ferring, Abbvie, Takeda, Prometheus Biosciences, Lilly, SorrisoPharma, Boehringer Ingelheim, Galapagos, BMS, AlfaSigma. M.T.D. received consultant fees from Pfizer and BMS. M.G. is a Member of the CICRA Advisory Board (Crohn's in Childhood Research Association). M.G. is currently involved in pharmaceutical trials sponsored by Abbvie (including M14-671). D.S.S. received lecturing fees from Takeda. M.V.R-B. received a consultant fee from Pfizer. O.H. received lectures/congress fees/consultancy from MSD, Abbvie, Takeda, Nutricia, Sandoz, Lilly, Pfizer. D.L.S.: Consultant: Pharming Pharm, Nestle. For the past 3 years, B.K. has received speaker fee, consultation fee, or research grant from Celltrion, Janssen, Abbvie, Takeda, Yuhan, Yungjin, JW Pharmaceutical, and Samsung Bioepis. H.H.U. has received research support or consultancy fees from J&J, Eli Lilly, Bristol Myers Squibb and AbbVie. H.H.U. is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) University of Oxford (HHU) and by The Leona M. and Harry B. Helmsley Charitable Trust. L.H.: received speaking fee from Abbvie. G.D.: Lectures/congress fees/consultancy: Nestlé Health Science and Pfizer. I.H. received lecture/consultation fee from Abbot, Pfizer, Nestle, Oktal-Pharma, Takeda. K.L.K.: received consultant/lecture fees from Abbvie, Biocodex and Ferring. P.H. is supported by an NRS Clinician Fellowship. L.N.: received consultant or advisory board honoraria by Takeda, Nestlè, Danone, Sanofi, Zealand.

Data Availability Statement

The data underlying this study are available in the paper and in its online Supporting Information. The data will be shared on reasonable request to the corresponding author.

References

1. P. F. van Rheenen, M. Aloi, A. Assa, et al., "The Medical Management of Paediatric Crohn's Disease: An ECCO-ESPGHAN Guideline Update," *Journal of Crohn's & Colitis* 15, no. 2 (2020): jjaa161, https://doi.org/10.1093/ecco-jcc/jjaa161.

2. O. Atia, Z. Shavit-Brunschwig, D. R. Mould, et al., "Outcomes, Dosing, and Predictors of Vedolizumab Treatment in Children With Inflammatory Bowel Disease (VEDOKIDS): A Prospective, Multicentre Cohort Study," *Lancet Gastroenterology & Hepatology* 8 (2023): 31–42.

3. A. Yerushalmy-Feler, G. Pujol-Muncunill, J. Martin-de-Carpi, et al., "Safety and Potential Efficacy of Escalating Dose of Ustekinumab in Pediatric Crohn Disease (The Speed-Up Study): A Multicenter Study From the Pediatric IBD Porto Group of ESPGHAN," *Journal of Pediatric Gastroenterology and Nutrition* 75, no. 6 (2022): 717–723.

4. S. Honap, S. Danese, and L. Peyrin-Biroulet, "Are All Janus Kinase Inhibitors for Inflammatory Bowel Disease the Same?," *Gastroenterology & Hepatology* 19, no. 12 (2023): 727–738.

5. S. Danese, S. Vermeire, W. Zhou, et al., "Upadacitinib as Induction and Maintenance Therapy for Moderately to Severely Active Ulcerative Colitis: Results From Three Phase 3, Multicentre, Doubleblind, Randomised Trials," *Lancet* 399 (2022): 2113–2128.

6. J. Panés, E. V. Loftus, P. D. R. Higgins, et al., "Induction and Maintenance Treatment With Upadacitinib Improves Health-Related Quality of Life in Patients With Moderately to Severely Active Ulcerative Colitis: Phase 3 Study Results," *Inflammatory Bowel Diseases* 29 (2023): 1421–1430.

7. S. Vermeire, S. Danese, W. Zhou, et al., "Efficacy and Safety of Upadacitinib Maintenance Therapy for Moderately to Severely Active Ulcerative Colitis in Patients Responding to 8 Week Induction Therapy (U-ACHIEVE Maintenance): Overall Results From the Randomised, Placebo-Controlled, Double-Blind, Phase 3 Maintenance Study," *Lancet Gastroenterology & Hepatology* 8 (2023): 976–989.

8. L. EV, Jr., J. Panés, A. P. Lacerda, et al., "Upadacitinib Induction and Maintenance Therapy for Crohn's Disease," *New England Journal of Medicine* 388 (2023): 1966–1980.

9. G. D'Haens, J. Panés, E. Louis, et al., "Upadacitinib Was Efficacious and Well-Tolerated Over 30 Months in Patients With Crohn's Disease in the CELEST Extension Study," *Clinical Gastroenterology and Hepatology* 20 (2022): 2337–2346.

10. E. A. Spencer, S. Bergstein, M. Dolinger, et al., "Single-Center Experience With Upadacitinib for Adolescents With Refractory Inflammatory Bowel Disease," *Inflammatory Bowel Diseases* 30 (2023): izad300, https://doi.org/10.1093/ibd/izad300.

11. A. Yerushalmy-Feler, C. Olbjorn, K. L. Kolho, et al., "Dual Biologic or Small Molecule Therapy in Refractory Pediatric Inflammatory Bowel Disease (DOUBLE-PIBD): A Multicenter Study From the Pediatric IBD Porto Group of ESPGHAN," *Inflammatory Bowel Diseases* 30 (2024): 159–166.

12. A. Kellar, M. T. Dolinger, E. A. Spencer, and M. C. Dubinsky, "Real-World Outcomes of Dual Advanced Therapy in Children and Young Adults With Inflammatory Bowel Disease," *Digestive Diseases and Sciences* 69, no. 5 (2024): 1826–1833.

13. A. S. Paller, B. Ladizinski, P. Mendes-Bastos, et al., "Efficacy and Safety of Upadacitinib Treatment in Adolescents With Moderate-To-Severe Atopic Dermatitis: Analysis of the Measure Up 1, Measure Up 2, and AD Up Randomized Clinical Trials," *JAMA Dermatology* 159 (2023): 526–535.

14. U.S. Food and Drug Administration. RINVOQ, (upadacitinib) drug label. (2022), https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211675s003lbl.pdf.

15. Y. Qian, E. M. Raymundo, S. Hao, et al., "Pharmacokinetics, Safety, Tolerability, and Exploratory Efficacy of Upadacitinib in Children With Severe Atopic Dermatitis," *Clinical Therapeutics* 46 (2024): 733–741.

16. A. Levine, S. Koletzko, D. Turner, et al., "Revised Porto Criteria for the Diagnosis of Inflammatory Bowel Disease in Children and Adolescents," *Journal of Pediatric Gastroenterology and Nutrition* 58, no. 6 (2014): 795–806.

17. D. Turner, A. M. Griffiths, T. D. Walters, et al., "Mathematical Weighting of the Pediatric Crohn's Disease Activity Index (PCDAI) and Comparison With Its Other Short Versions," *Inflammatory Bowel Diseases* 18, no. 1 (2012): 55–62.

18. A. Levine, A. Griffiths, J. Markowitz, et al., "Pediatric Modification of the Montreal Classification for Inflammatory Bowel Disease: The Paris Classification," *Inflammatory Bowel Diseases* 17, no. 6 (2011): 1314–1321.

19. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and National Heart, Lung, and Blood Institute, "Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report," *Pediatrics* 128, no. 5 (2011): S213–S256.

20. S. Friedberg, D. Choi, T. Hunold, et al., "Upadacitinib Is Effective and Safe in Both Ulcerative Colitis and Crohn's Disease: Prospective Real-World Experience," *Clinical Gastroenterology and Hepatology* 21, no. 7 (2023): 1913–1923.

21. A. T. Elford, M. Bishara, N. Plevris, et al., "Real-World Effectiveness of Upadacitinib in Crohn's Disease: A UK Multicentre Retrospective Cohort Study," *Frontline Gastroenterology* 15, no. 4 (2024): 297–304.

22. R. Chugh, M. B. Braga-Neto, T. W. Fredrick, et al., "Multicentre Real-World Experience of Upadacitinib in the Treatment of Crohn's Disease," *Journal of Crohn's & Colitis* 17, no. 4 (2023): 504–512.

23. C. Niu, J. Zhang, M. Napel, et al., "Systematic Review With Meta-Analysis: Efficacy and Safety of Upadacitinib in Managing Moderate-To-Severe Crohn's Disease and Ulcerative Colitis," *Clinical Drug Investigation* 44, no. 6 (2024): 371–385.

24. M. Attauabi, C. Steenholdt, A. Poulsen, et al., "Network Meta-Analysis: Comparative Onset of Early Effect of Biologics and Small Molecules in Moderately to Severely Active Luminal Crohn's Disease," *Alimentary Pharmacology & Therapeutics* 60, no. 2 (2024): 124–143.

25. L. Peyrin-Biroulet, E. Louis, E. V. Loftus, Jr., et al., "Quality of Life and Work Productivity Improvements With Upadacitinib: Phase 2b Evidence From Patients With Moderate to Severe Crohn's Disease," *Advances in Therapy* 38, no. 5 (2021): 2339–2352.

26. J. F. Colombel, A. P. Lacerda, P. M. Irving, et al., "Efficacy and Safety of Upadacitinib for Perianal Fistulizing Crohn's Disease: A Post Hoc Analysis of 3 Phase 3 Trials," *Clinical Gastroenterology and Hepatology* (2024): S1542-3565(24)00860, https://doi.org/10.1016/j.cgh.2024.08.032.

27. S. Bhatnagar, L. Schlachter, D. Eckert, et al., "Pharmacokinetics and Exposure-Response Analyses to Support Dose Selection of Upadacitinib in Crohn's Disease," *Clinical Pharmacology and Therapeutics* 116 (2024): 1240–1251, https://doi.org/10.1002/cpt.3359.

28. Y. Miyatani, D. Choi, N. K. Choi, and D. T. Rubin, "Dual-Targeted Therapy With Upadacitinib and Ustekinumab in Medically Complex Crohn's Disease," *Digestive Diseases and Sciences* 69, no. 2 (2024): 355–359.

29. L. Peyrin-Biroulet, R. Panaccione, E. Louis, et al., "Upadacitinib Achieves Clinical and Endoscopic Outcomes in Crohn's Disease Regardless of Prior Biologic Exposure," *Clinical Gastroenterology and Hepatology* 22, no. 10 (2024): S1542-3565(24)00253–2, https://doi.org/10.1016/j.cgh.2024.02.026.

30. J. F. Colombel, T. Hisamatsu, R. Atreya, et al., "Upadacitinib Reduces Crohn's Disease Symptoms Within the First Week of Induction Therapy," *Clinical Gastroenterology and Hepatology* 22, no. 8 (2024): 1668–1677.

31. S. Ghosh, B. G. Feagan, R. S. Parra, et al., "Impact of Upadacitinib Induction and Maintenance Therapy on Health-Related Quality of Life, Fatigue, and Work Productivity in Patients With Moderately-to-severely Active Crohn's Disease," *Journal of Crohn's & Colitis* 18, no. 11 (2024): jjae083, https://doi.org/10.1093/ecco-jcc/jjae083.

32. J. Pokryszka, S. Reinisch, C. Primas, G. Novacek, and W. Reinisch, "Induction Efficacy of Upadacitinib in Therapy-Refractory Crohn's Disease: A Retrospective Case Series," *Clinical Gastroenterology and Hepatology* 21, no. 2 (2023): 532–534.e3.

33. C. Traboulsi, F. Ayoub, A. Silfen, T. G. Rodriguez, and D. T. Rubin, "Upadacitinib Is Safe and Effective for Crohn's Disease: Real-World Data From a Tertiary Center," *Digestive Diseases and Sciences* 68, no. 2 (2023): 385–388.

34. European Medicines Agency, "EMA Recommends Measures to Minimise Risk of Serious Side Effects With Janus Kinase Inhibitors for Chronic Inflammatory Disorders," 2022, https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic-inflammatory-disorders.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.