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ORIGINAL RESEARCH ARTICLE

Effectiveness and Safety of Ustekinumab in Pediatric Ulcerative Colitis: A Multi-center Retrospective Study from the Pediatric IBD Porto Group of ESPGHAN

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Abstract

Background and Objectives Current data on ustekinumab therapy in children with ulcerative colitis (UC) or unclassified inflammatory bowel disease (IBDU) are limited. We aimed to evaluate the effectiveness and safety of ustekinumab in pediatric UC and IBDU.

Methods This multicenter retrospective study included 16 centers affiliated with the IBD Interest and Porto groups of ESPGHAN. Children with UC or IBDU treated with ustekinumab were enrolled. Demographic, clinical, laboratory, endoscopic, and imaging data as well as adverse events were recorded. Analyses were all based on the intention-to-treat principle.

Results Fifty-eight children (39 UC and 19 IBDU, median age 14.5 [IQR 11.5–16.5] years) were included. All had failed biologic therapies, and 38 (66%) had failed two or more biologics. Corticosteroid-free clinical remission (CFR) was observed in 27 (47%), 33 (57%), and 37 (64%) children at 16, 26, and 52 weeks, respectively. Normalization of C-reactive protein and calprotectin < 150 µg/g were achieved in 60% and 52%, respectively, by 52 weeks. Endoscopic and radiologic remissions were reached in 8% and 23%, respectively. The main predictors of CFR were diagnosis of UC compared with IBDU (hazard ratio [HR] 2.2, 95% CI 1.03–4.85; $p = 0.041$) and no prior vedolizumab therapy (HR 2.1, 95% CI 1.11–4.27; $p = 0.023$). Ustekinumab serum levels were not associated with disease activity. Adverse events were recorded in six (10%) children, leading to discontinuation of the drug in three.

Conclusion Based on these findings, ustekinumab appears as an effective therapy for pediatric refractory UC and IBDU. The potential efficacy should be weighed against the risks of serious adverse events.

1 Introduction

Current evidence supports the use of anti-tumor necrosis factor (TNF) regimens as first-line biologics in children with ulcerative colitis (UC) after failing 5-ASA and thiopurines [1]. While infliximab and adalimumab are currently the only biologics approved for pediatric IBD, the primary non-response rate is approximately 30%, and a significant proportion of the responders experience loss of response over time [2–4]. Although not approved for the pediatric population, real-world data support the use of vedolizumab in pediatric UC, with a corticosteroid-free remission (CFR) rate of 42% at week 14 [5].

Ustekinumab (STELARA®), a monoclonal antibody targeting interleukins 12 and 23, is effective for inducing and maintaining remission in adults with Crohn's disease [6–8] as well as those with UC [9]. The UNIFI study on adults with UC observed clinical remission rates of 15% and 44% at weeks 8 and 44, respectively. The CFR rate at week 152 was approximately 50% [10]. Those results were supported by several real-world studies [11–15]. Data on the effectiveness of ustekinumab in pediatric UC and unclassified IBD (IBDU), however, are very limited. A single study reported that 24% and 44% of 25 children with UC were on CFR at weeks 26 and 52, respectively [16]. Given such paucity of data on ustekinumab therapy in the pediatric UC population and the clear need for innovative therapies in refractory pediatric IBD, the aim of this study

Extended author information available on the last page of the article

was to evaluate the effectiveness and safety of ustekinumab in children with UC and IBDU.

2 Methods

2.1 Study Design and Population

This was a retrospective cohort study from 16 centers affiliated with the Pediatric IBD Interest and Porto groups of ESPGHAN. Included were children and adolescents (≤18 years of age) diagnosed with UC or IBDU according to the revised Porto criteria and current guidelines [1, 17] treated with ustekinumab (at least one dose).

2.2 Data Collection

We collected demographic and clinical data on UC characteristics, disease extent and severity defined according to the Paris classification [18], disease activity as measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI) [19], past and concomitant therapy, clinical course, hospitalizations, disease exacerbations, surgeries, laboratory results, and imaging and endoscopic findings. Adverse events were recorded.

2.3 Outcomes

The primary outcome of the study was CFR following the initiation of ustekinumab over 52 weeks. The secondary outcomes were clinical remission, clinical response at 16 weeks, C-reactive protein (CRP) level < 5 mg/L, fecal calprotectin (FC) < 150 µg/g, endoscopic and radiologic evidence of remission when available, hospitalizations, disease exacerbations, need for IBD-related surgery during the follow-up, durability of therapy, and adverse events.

Clinical remission was defined as a PUCAI <10. Clinical response was defined as reduction of the PUCAI by > 20 points. Laboratory remission was defined as CRP < 5 mg/L and FC < 150 µg/g. Radiologic remission was defined as radiological global assessment by a local expert of complete remission at bowel ultrasound or magnetic resonance enterography. Endoscopic healing was defined as a Mayo endoscopic score [20] of 0 at colonoscopy during the follow-up. Endoscopic and radiologic remission were calculated in the intention-to-treat group (ITT) using non-response imputation for children that discontinued therapy during follow-up. Disease exacerbation was defined as PUCAI ≥10.

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 means of the Chi-square test or the Fisher's Exact test, as appropriate, while continuous variables were compared with the Mann-Whitney test. Kaplan-Meier curves were used to describe the outcomes during the follow-up period. The log-rank test was applied for categorical variables, while univariate Cox regression was applied for continuous variables. These tests were used to study the crude association between each predictor and the studied outcomes. Multivariate Cox regression was used to study the association between variables that were found to be significant in the univariate analysis. All analyses were performed in the ITT population. Children that discontinued therapy were considered treatment failures and they were imputed as non-response, while missing data were imputed according to the last observation carried forward method. A generalized estimating equation model was used for the repeated measure analysis. All statistical tests were 2-tailed; a p value <0.05 was considered statistically significant. SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA: IBM Corp.) was used for all statistical analyses.

3 Results

Fifty-eight children were included, of whom 39 (67.2%) were diagnosed with UC and 19 (32.8%) with IBDU. Their median [IQR] age was 14.5 [11.5–16.5] years at the initiation of ustekinumab therapy (Table 1). The median [IQR] duration of the follow-up was 12.8 [5.1–26.3] months. Before having undergone ustekinumab therapy, 50 (86.2%) children had been treated with immunomodulators. All 58 patients were treated with biologic agents: 20 (34.5%) failed one biologic agent, 28 (48.3%) failed two biologic agents, and 10 (17.2%) failed three biologic agents. The median PUCAI at the initiation of ustekinumab therapy was 45 [31.3–55].

The induction and maintenance doses of ustekinumab are presented in Supplementary Table 1 (see electronic supplementary material [ESM]). Ustekinumab was provided in combination therapy in 47 (81%) children, as follows: corticosteroids (31 children, 53.4%), 5-aminosalicylic acid (5-ASA) (26 children, 44.8%), thiopurines (16 children, 27.6%), methotrexate (3 children, 5.2%), and others (adalimumab, golimumab, vedolizumab, cyclosporin, and tacrolimus).

Table 1 Demographic and clinical characteristics of the study cohort

	All ($N = 58$)	Absence of corticosteroid-free remission ($N = 21$)	Corticosteroid-free remission ($N = 37$)	p-value
Age at diagnosis of IBD (years)	10.9 (6.8–13.7)	13.5 (10.6–14.8)	8.9 (5.7–12.2)	0.003
Age at ustekinumab therapy (years)	14.5 (11.5–16.5)	15.9 (13.5–16.9)	13.2 (10–15.9)	0.009
Females	34 (58.6%)	12 (57.1%)	22 (59.5%)	0.863
IBD type				0.514
UC	39 (67.2%)	13 (61.9%)	26 (70%)	
IBDU	19 (32.8%)	8 (38.1%)	11 (29.7%)	
Caucasian origin	43 (74.1%)	15 (71.4%)	28 (75.7%)	0.723
Family history of IBD	19 (32.8%)	9 (42.9%)	10 (27%)	0.217
Disease extent				0.349
Proctitis	1 (1.7%)	1 (4.8%)	0	
Left-sided colitis	8 (13.8%)	2 (9.5%)	6 (16.2%)	
Extensive colitis	4 (6.9%)	3 (14.3%)	1 (2.7%)	
Pancolitis	45 (77.6%)	15 (71.4%)	30 (81.1%)	
Disease severity				0.136
Never severe	24 (41.4%)	6 (28.6%)	18 (48.6%)	
Ever severe	34 (58.6%)	15 (71.4%)	19 (51.4%)	
Upper GI involvement	4 (6.9%)	2 (9.5%)	2 (5.4%)	0.552
EIM	6 (10.3%)	2 (9.5%)	4 (10.8%)	0.877
Previous therapies				
EEN	5 (8.6%)	2 (9.5%)	3 (8.1%)	0.853
PEN	8 (13.8%)	2 (9.5%)	6 (16.2%)	0.477
Corticosteroids	57 (98.3%)	20 (95.2%)	37 (100%)	0.362
5-ASA	55 (94.8%)	21 (100%)	34 (91.9%)	0.295
Thiopurines	50 (86.2%)	18 (85.7%)	32 (86.5%)	0.935
Methotrexate	7 (12.1%)	4 (19%)	3 (8.1%)	0.219
Infliximab	48 (82.8%)	16 (76.2%)	32 (86.5%)	0.318
Adalimumab	22 (37.9%)	7 (33.3%)	15 (40.5%)	0.587
Vedolizumab	31 (53.4%)	16 (76.2%)	15 (40.5%)	0.009
Golimumab	4 (6.9%)	0	4 (10.8%)	0.286
Etrolizumab	1 (1.7%)	0	1 (2.7%)	> 0.999
Cyclosporin	1 (1.7%)	1 (4.8%)	0	0.362
Tacrolimus	1 (1.7%)	0	1 (2.7%)	> 0.999
Thalidomide	2 (3.4%)	0	2 (5.4%)	0.529
Antibiotics	22 (37.9%)	9 (42.9%)	13 (35.1%)	0.585
Tofacitinib	5 (8.6%)	2 (9.5%)	3 (8.1%)	> 0.999
IBD duration (years)	2.6 (0.8–4.3)	2.3 (1.8–3.9)	2.5 (0.6–4.5)	0.697

Values are given as median (interquartile range) and n (%)

5-ASA 5-aminosalicylic acid, *EEN* exclusive enteral nutrition, *EIM* extra-intestinal manifestations, *GI* gastrointestinal, *IBD* inflammatory bowel disease, *IBDU* unclassified inflammatory bowel disease, *PEN* partial enteral nutrition, *UC* ulcerative colitis

Twenty-three (39.7%) of the patients underwent escalation of ustekinumab dosage during the follow-up period: 18 (78.3%) underwent interval shortening, one underwent dose elevation, three underwent both interval shortening and dose elevation, and one underwent re-induction. Thirteen patients (57%) had clinical or biomarker response to dose escalation.

3.1 Outcomes

Twenty-four (41.4%) children discontinued ustekinumab therapy at a median duration of 5 [3.4–10.3] months after initiation. The reasons for discontinuation were non-response in 21 (87.5%) and adverse events in three (12.5%). Following discontinuation, 10 (41.7%) patients underwent colectomy.

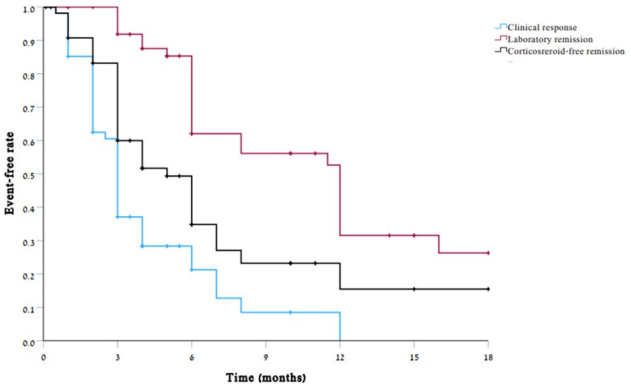

Fig. 1 Time to clinical response, corticosteroid-free clinical remission, and laboratory remission

CFR was observed in 27 (46.6%), 33 (56.9%), and 37 (63.8%) children, at 16, 26, and 52 weeks, respectively (Fig. 1). Clinical remission was observed in 29 (50%), 33 (56.9%), and 37 (63.8%) children at 16, 26, and 52 weeks, respectively, and clinical response in 39 (67.2%) children at 16 weeks (Fig. 1). The decrease in PUCAI during the follow-up is presented in Supplementary Table 2 (see ESM). Of the 31 children treated with corticosteroids at the initiation of ustekinumab therapy, 26 (83.9%) were weaned within a median of 3 [2–4] months. None of them needed re-treatment with corticosteroids during the follow-up. The rates of CFR in patients treated with corticosteroids at baseline were 39%, 52%, and 61% at weeks 16, 26, and 52 compared with 56%, 63%, and 67% among those that were not treated with steroids ($p = 0.199$, $p = 0.384$, $p = 0.671$, respectively). Overall, 19/31 (57.6%) children that were under corticosteroid therapy at baseline and 18/27 (66.7%) that were not treated with corticosteroids achieved CFR ($p = 0.671$).

CRP and FC levels at 52 weeks were available in 32 (55%) and 25 (43%) children, respectively. Normal CRP and FC <150 µg/g were achieved at 52 weeks in 45 (77.6%) and 36 (62%) children, respectively. Among 33 children with elevated CRP and 46 with elevated FC at baseline, these rates were 60.1% and 52.2%, respectively. Laboratory remission was achieved in 11 (19%), 16 (36.2%), and 25 (51.7%) children at 16, 26, and 52 weeks, respectively. The longitudinal changes in CRP, FC, serum hemoglobin, albumin, and erythrocyte sedimentation rate (ESR) are presented in Supplementary Table 2 (see ESM). Six children (10.3%) underwent colectomy at a median duration of 3 [1–9] months while on ustekinumab therapy, three of them had severe UC at the initiation of ustekinumab. Eleven children (19%) had IBD-related hospitalization. Disease exacerbation among remitters was observed in 13 (37.1%) children after a median of 5 [4–9] months during follow-up. Endoscopic and radiologic remission were observed in 3/16 (19%) and 7/10 (70%) children that underwent endoscopic or radiologic evaluation, respectively. Endoscopic and radiologic remission were reached in 8.1% and 23.3%, respectively, among the ITT group, using non-response imputation for children that failed therapy. Eight patients had a Mayo score of 1 at endoscopic follow-up.

3.2 Predictors of Outcomes

The variables associated with the achievement of CFR were diagnosis of UC compared with IBDU (HR 2.24, 95% CI 1.03–4.85; $p = 0.041$), lack of previous vedolizumab therapy (HR 2.18, 95% CI 1.11–4.27; $p = 0.023$), and a history of corticosteroid-resistant disease (HR 4.29, 95% CI 1.58–11.65; $p = 0.004$). Other variables, such as age, sex, disease duration and phenotype, clinical and endoscopic severity, extra-intestinal manifestations, past therapies (except vedolizumab), dosing regimen, and combination therapy were not associated with clinical and laboratory remission. While the six patients that received an induction dose of 130 mg were not prone to failure (5/6 responded to ustekinumab), all these patients required dose escalation of ustekinumab. The clinical response rate at week 16 was correlated with the CFR rate at week 52: 17 of 19 (89%) non-responders did not achieve CFR, and 35 of 39 (90%) responders achieved CFR ($p < 0.001$). A multivariate analysis adjusted to age, disease type, previous therapy with vedolizumab, and steroid resistance revealed that none served as an independent predictor of CFR.

3.3 Ustekinumab Serum Levels

Ustekinumab levels were available for 22 (38%) patients (49 measurements altogether). The median [IQR] levels were 4.1 [1.9–5.1], 2.7 [1.6–6.8], and 2.6 [2.1–5.4] µg/mL at weeks 16, 26, and 52, respectively. None of the patients had evidence of anti-drug antibodies. No difference was observed between 4-week and 8-week dose intervals (3.4 [2.4–4.5] vs 2.6 [1.4–6], $p = 0.435$). All four patients with measurements below 1 µg/mL had active disease. However, serum levels of patients in clinical remission were not different from those of patients with active disease (3.7 [2.6–5.7] vs 5.1 [0.4–6.2] µg/mL, respectively; $p = 0.872$). Among the nine patients that underwent dose escalation and had available repeated measurements of drug levels before and after dose escalation, 6 (67%) had an increase in drug levels post-escalation (from 4.7 [2.3–5.1] to 8.9 [4.8–9.7] µg/mL). Of these six patients, four responded to dose escalation. The serum levels at week 16 were not predictive of CFR at 52 weeks.

Table 2 Adverse events

Adverse event	Clinical details	Age, y	Sex	IBD type	Duration of ustekinumab therapy	Combination therapy	Corticosteroid-free clinical remission	Discontinuation of therapy due to adverse event
Acute diarrhea leading to demise	N/A	16	Male	IBDU	19 months	Steroids and methotrexate	Yes	Yes
Interstitial nephritis	Resolved after steroid treatment, normal renal function after 6 months	12	Male	UC	1 dose	5-ASA	No	Yes
Hypersensitivity reaction	Flushing and vomiting during infusion	14	Female	UC	1 dose	5-ASA, azathioprine	Yes	Yes
Breast abscess	Resolution after drainage	13	Female	UC	38 months	None	Yes	No
Injection-site reaction	N/A	16	Male	UC	10 months	5-ASA, azathioprine	No	No
Cytomegalovirus infection	N/A	3	Male	UC	6 months	Azathioprine	Yes	No

5-ASA 5-aminosalicylic acid, *IBDU* unclassified inflammatory bowel disease, *N/A* not available, *UC* ulcerative colitis

3.4 Adverse Events

Adverse events that were potentially related to ustekinumab therapy were reported in 6 (10.3%) children (Table 2), leading to discontinuation of therapy in three. The adverse events included interstitial nephritis, hypersensitivity reaction, breast abscess, injection-site reaction, cytomegalovirus infection, and one death due to an acute episode of severe diarrhea in an adolescent male. No further details were provided on the last adverse event due to privacy policy.

4 Discussion

In this retrospective cohort of children with UC and IBDU treated with ustekinumab, CFR was achieved in 47%, 57%, and 64% at 16, 26, and 52 weeks, respectively. There was a high frequency (84%) of corticosteroid withdrawal, in addition to a significant improvement of biomarkers. The rates of endoscopic and radiologic remission were low. Compared with children with IBDU, children with UC and those naïve to vedolizumab had a higher probability of achieving CFR. While the total rate of adverse events was low, several of the reported adverse events were serious; nonetheless, the causality relationship with the drug remains uncertain.

Ustekinumab is recognized as an effective therapy for UC in the adult population. The UNIFI studies [9] reported a clinical remission rate of 16% at week 8 and 38–44% at week 44. A significant benefit of the therapy was also observed as early as week 2 [21]. The long-term efficacy of ustekinumab maintenance in patients with UC was confirmed through 3 and 4 years [10, 22]. Several real-world studies supported the use of ustekinumab in UC, reporting CFR rates of 20–40% at weeks 8–16 [11–14, 23–25] and 32–50% at weeks 26–52 [11–13, 23, 25]. In pediatric UC, Dhaliwal et al. [16] reported that 24% and 44% of 25 children were on CFR at weeks 26 and 52, respectively. A comparable remission rate was observed in our cohort. None of the patients in this cohort have lost CFR under ustekinumab therapy. This is in line with the data from the long-term extension of the UNIFI study [10], which showed loss of response to ustekinumab mostly beyond the first year of therapy.

Since over 50% of our patients were steroid-dependent and 53% were treated with corticosteroids at the initiation of ustekinumab, weaning off steroids was another essential target. Eighty-four percent of the patients in our cohort successfully weaned steroids within 3 months after the initiation of ustekinumab. Other studies reported a comparable rate of withdrawal from corticosteroids under ustekinumab therapy [9, 12]. Importantly, the patient population in our series and in most of those studies was characterized by extensive and severe UC that was refractory to various therapies. Twenty-eight (48%) of our patients had failed more than one biologic agent, and 10 (17%) had failed three different biologic agents. The concomitant use of corticosteroids did not affect the rate of CFR in our cohort.

A potential explanation for this observation could be that patients that were treated with concomitant corticosteroids had more severe disease. The potential therapeutic benefit of corticosteroids, which was not observed in this cohort, should be weighted against the risk immunosuppression.

There are currently no data that predict response to ustekinumab therapy in UC. Our results revealed that children with UC had a higher rate of CFR compared with children with IBDU (HR 2.24), as well as children naïve to vedolizumab (HR 2.18), and those with steroid-resistant disease (HR 4.29). The benefit of ustekinumab in UC compared with IBDU was surprising, considering that the drug was approved for adults with Crohn's disease before its approval for UC, and that IBDU shares common features with Crohn's disease. The advantage of ustekinumab in steroid-resistant patients may originate from the higher rate of vedolizumab-naivety in those patients (86% vs 41%, $p = 0.027$). Importantly, the clinical benefit of ustekinumab therapy was not associated with either the dosing regimen or with combination therapy. Dhaliwal et al. [16] also observed that children who were naïve to vedolizumab had a higher probability to achieve CFR compared with children who failed anti-TNF agents and vedolizumab (odds ratio 17.4). Failure of vedolizumab therapy may be suggestive of more resistant disease, with a lower likelihood to respond to ustekinumab as well.

There was also an improvement in objective laboratory measures under ustekinumab therapy in our cohort. Normalization of CRP and decline of FC to <150 µg/g at week 52 were achieved in 60% and 52% of children, respectively. A significant improvement was also observed in the levels of hemoglobin, albumin, and ESR. Some studies also reported a significant decrease in CRP and FC levels in adults [9, 10, 12], but mixed results were observed by others [13, 15].

Endoscopic and radiologic endpoints are now recognized as essential therapeutic goals. The rates of endoscopic and radiologic remission were 8% and 23%, respectively, among the ITT population. Our findings are comparable to other studies that addressed these outcomes. The week 44 rate of endoscopic improvement in the UNIFI study was 51% among patients treated every 8 weeks and 44% among those treated every 12 weeks [9]. Fumery et al. [11] reported a significant decrease in the Ulcerative Colitis Endoscopic Index of Severity and in the mean Mayo endoscopic subscore for patients under ustekinumab therapy. Other studies observed endoscopic improvement in 36–44% of the patients and mucosal healing in 22–28% [12, 13, 16].

Adult studies have shown a positive association between ustekinumab serum concentrations and clinical remission [9] in addition to histological remission and histo-endoscopic mucosal improvement [26]. In our pediatric study, ustekinumab serum levels were comparable between patients in clinical remission and those with active disease, as was also observed in another pediatric population [16]. While the median trough levels in Dhaliwal et al.'s study were higher with 4 versus 8 weeks of dosing, we found no difference between the dosing regimens [16]. This could be attributed to the fact that 29% of our patients who received 4 weeks of dosing had been treated with a lower dose (45 mg). However, greater exposure was not associated with a superior rate of clinical remission in either study. Dose intensification was required in 40% of our patients, and the response rate to intensification was relatively high, as was observed by others [24].

The frequency of discontinuation of ustekinumab therapy was 13–44% in numerous studies [10–13, 15, 27, 28], with the main reasons for discontinuation being non-response and loss of response. Those rates are comparable to our study, in which nearly half of the children discontinued ustekinumab therapy, mainly due to non-response. This rate should be included in the decision-making algorithm when considering ustekinumab therapy for children with UC.

Ustekinumab has a generally favorable safety profile [9, 10, 12–14, 16, 25, 29]. Worsening of UC, nasopharyngitis, and upper respiratory tract infection are the most frequently reported adverse events [10], while discontinuation of the therapy due to adverse events is infrequent [11, 13, 15, 29]. The safety profile of ustekinumab in our study is similar to those reported for the adult population. However, the serious adverse events that were observed in our study mandate a cautious approach when considering ustekinumab therapy for children. The patient that died while on ustekinumab therapy was also treated with corticosteroids and methotrexate. This raises concerns about the concomitant use of multiple immunosuppressive agents in patients with refractory disease. Nonetheless, the causality relationship between several adverse events and the drug remains uncertain.

4.1 Limitations of the Study

The main limitation is that the definition of clinical remission was based upon clinical activity index, although objective measures (biomarkers as well as radiologic and endoscopic endpoints) were evaluated as well. Due to the retrospective nature of the study, not all of the results of the pharmacokinetics of ustekinumab were available. Another limitation is the lack of complete endoscopic and radiographic follow-up data. Lastly, safety cannot be reliably evaluated in a retrospective study.

5 Conclusions

This largest-to-date multicenter study demonstrated that ustekinumab is effective in children with refractory UC and IBDU in terms of clinical, biomarker, and, to a lesser extent, endoscopic outcomes. The potential efficacy should be weighed against the risk of serious adverse events.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40272-024-00631-z.

Declarations

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Conflicts of Interest In the last 3 years DT received consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, Shaare Zedek Medical Center, Hospital for Sick Children, Ferring, Abbvie, Takeda, Prometheus Biosciences, Lilly, Roche, ThermoFisher, BMS, SorrisoPharma. KLK has received consultation fees from Abbvie, Biocodexa and Tillotts Pharma and research grants from Pediatric Research Foundation (Finland) and Helsinki University Hospital Research Fund. In the past 3 years, Ben Kang has recieved speaker fees, consultation fees, or research grants from Celltrion, Janssen, Abbvie, Takeda, Yuhan, Yungjin, JW Pharmaceutical, and Samsung Bioepis.

Ethics Approval This study was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center (TLV-23-0114) and equivalent committees of all contributing centers.

Consent to Participate Informed consent was waived for this retrospective and anonymized investigation.

Consent for Publication Not applicable.

Availability of Data and Materials Not applicable.

Code Availability Not applicable.

Author Contributions AYF and SC: designed the study, initiated the concepts, wrote the paper. All authors: significant contribution towards recruiting patients. All authors approved the final version of the manuscript.

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