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Experience Using Ustekinumab in Pediatric Patients with Medically Refractory Crohn's Disease

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Abstract

Introduction: Ustekinumab (UST), a human monoclonal antibody against interleukin-12 and 23, is approved to treat adult patients with psoriasis or Crohn's Disease (CD). Outcomes data for off-label use in pediatric patients with CD are limited.

Aim: We conducted a retrospective cohort study to analyze the long-term efficacy of UST, including dose adjustments, in the treatment of pediatric patients with medically refractory CD. Adverse events were documented.

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Conflicts of Interest
The remaining authors have no conflicts of interest.

Methods: We identified 40 pediatric patients with CD treated with UST between January 1, 2016 and December 31, 2019. Electronic medical records were reviewed for demographics, Paris Classification, significant comorbidities, previous CD therapy, adverse events after initiation, and surveillance markers at the time of their first dose and most recent clinic visit. A validated abbreviated pediatric CD activity index (aPCDAI) was used to assess response to therapy.

Results: Thirty-eight pediatric patients with CD, including 34.2% with stricturing or penetrating disease, were analyzed after initiation of treatment with UST. Median age at diagnosis of CD was 12.5 years, and median age at UST induction was 17.2 years. No patients were anti-TNF naïve, and 34.2% were previously exposed to two or more anti-TNF agents. At time of last follow-up, 84.2% of patients remained on UST for a median duration on UST of 62.1 weeks, and 60.5% achieved clinical remission. Patients had significant improvement in aPCDAI scores, clinical remission rates, albumin, and hematocrit, and 89.5% of patients had no significant adverse events. Similar results were observed among those who required dose adjustment, including 61.1% achieving clinical remission, and among those with perianal disease, including 38.5% achieving clinical remission.

Conclusion: Our data suggest that, within our cohort of pediatric patients with CD, UST has long-term efficacy with no observed safety concerns. Dose adjustment may be helpful in achieving clinical remission.

Keywords

Introduction

Ustekinumab (UST) is a human monoclonal antibody against interleukin (IL)-12 and 23 that is effective in achieving and maintaining remission in adult patients with Crohn's Disease (CD) (1). The UNITI trials demonstrated clinical response by week 6 in 51.7% of anti-tumor necrosis factor alpha (TNF-α) naïve patients and 34.3% of TNF-α exposed patients (2, 3). Given its efficacy in adult populations, UST is currently used off-label to treat pediatric patients with CD who are refractory to conventional first-line therapies. However, data on safety and efficacy in the pediatric population are limited. Case reports and small case series noted clinical and biomarker improvements in up to 50% of patients (4–6). In a retrospective cohort study by Chavannes *et al.* (2019), 44 pediatric patients with moderate to severe CD demonstrated a 40% clinical remission rate at one-year, with statistically significant improvements in body mass index (BMI) Z-scores among patients with growth failure (7). Similarly, a recent study by Dayan *et al.* (2019) reported a 40% steroid-free clinical remission rate at one-year in pediatric patients with CD who were previously refractory to TNF-α blockade (8).

To expand these results in the pediatric population, we report our experience with using UST in pediatric patients with CD followed at two affiliated tertiary care centers. We evaluated efficacy using biomarkers, anthropomorphic data, and abbreviated pediatric CD activity index (aPCDAI) scores, and compared these endpoints with endpoints in patients

who required dose adjustments and patients who had perianal disease. We also noted any significant adverse events while on UST.

Methods

Study Design

We conducted a retrospective cohort study at the University of California San Francisco (UCSF) Benioff Children's Hospitals in San Francisco and Oakland. We identified 40 pediatric patients who were 21 years or younger at time of UST induction and last follow-up, received their first dose after January 1, 2016 and had at least one clinical follow-up visit while on the medication. Data were collected until the medication was discontinued or through December 31, 2019 if the medication was continued. Patients with Ulcerative Colitis (UC) or Inflammatory Bowel Disease-Unclassified (IBD-U) were excluded from the study. All patients were followed by a board-certified pediatric gastroenterologist at either the UCSF Pediatric Inflammatory Bowel Disease Center in San Francisco or Oakland, and all medication changes were at the discretion of the treating physician. The UCSF Benioff Children's Hospital Institutional Review Board (IRB) approved data collection for this study (IRB #13–12137).

Data Collection

Data extracted from the electronic medical record included: demographics (age, race, ethnicity, and gender); disease course (prior CD therapies, Paris classification (9), prior abdominal surgery); comorbidities; and UST treatment regimen. All patients received a single intravenous (IV) induction dose of 260 mg, 390 mg, or 520 mg per weight-based dosing guidelines (10). Maintenance doses were administered subcutaneously, and dosing interval or need for re-induction was based on clinician's judgment of disease severity and medication response. We collected data on changes in dosing frequency and UST IV re-induction.

Outcome markers included changes in aPCDAI scores, hematocrit (Hct), C-reactive protein (CRP), and albumin (Alb). The aPCDAI is a previously validated clinical tool to gauge CD activity in the pediatric population, with scores < 10 indicating clinical remission, 10 to 15 mild disease, 15 to 25 moderate disease, and > 25 severe disease (11). We evaluated changes in the aPCDAI scores over the time period that each patient received UST, and calculated the percent of patients who achieved clinical remission at the end of our study period. Anthropomorphic measurements with Z-scores on height, weight, and body mass index (BMI) were collected to evaluate nutritional outcomes while on UST. The baseline values for these variables at UST induction were compared with those at the time of latest follow-up. As a secondary marker of disease activity, we also gathered data on IBD-related hospitalizations, IBD flares, and need for IBD-related surgery while on UST. We also gathered data on adverse events including anaphylaxis, infusion site reactions, and infection. Adverse outcomes after starting UST judged to be due to the patient's CD course were documented separately.

Statistical Analysis

Data were assembled in a secure REDCap (Research Electronic Data Capture) server (12) and analyzed using STATA SE 15.1. Univariate analyses were utilized to examine the effectiveness of UST as it pertains to each outcome variable. For all continuous variables, median and interquartile ranges (IQR) were calculated. All parametric and relative non-parametric values were compared using either a two-tailed paired t-test or Wilcoxon signed-rank, respectively, as appropriate. A *p*-value < 0.05 was considered to be statistically significant.

Results

Patient Demographics

We identified 40 pediatric patients who received UST for CD. Two patients were excluded from the final analysis as they were lost to follow-up and therefore did not meet the full inclusion criteria. The median age at diagnosis was 12.5 years [IQR: 10.2 – 15.0], and the median age at initiation of UST was 17.2 years [IQR: 14.5 – 18.8] (Table 1). The majority of patients had ileocolonic disease (N = 27, 71.1%), and 7 (18.4%) patients had growth impairment as defined by the Paris Classification (9). Thirteen (34.2%) patients had complicated CD, including stricturing (N = 7, 18.4%), penetrating (N = 4, 10.5%), and both stricturing and penetrating disease (N = 2, 5.3%). Perianal disease, defined as presence of fistulae, anal canal ulcers, or abscesses (9), was present in 13 (34.2%) patients. Extra-intestinal manifestations of IBD were present in 23 (60.5%) patients; the most common manifestation was oral ulcers (N = 5, 13.2%). Eleven (28.9%) patients had prior IBD-related abdominal surgery.

All patients failed prior biologic therapy for CD, including 13 (34.2%) patients who were exposed to two or more anti-TNF agents (Table 2). Five (13.2%) patients had also failed anti-integrin therapy with vedolizumab. At the time of induction, 7 (18.4%) patients were on oral corticosteroids, and 29 (76.3%) patients had previously trialed at least one but no more than three immunomodulators, never simultaneously, including 25 (65.8%) who had tried methotrexate, and 16 (42.1%) who had tried a thiopurine at any time prior to starting UST (Table 2).

Ustekinumab Dosing

Patients received an intravenous infusion of either 260 mg (N = 18, 47.4%), 390 mg (N = 16, 42.1%), or 520 mg (N = 4, 10.5%) as an induction dose. For maintenance dosing, all patients were started on 90mg subcutaneous injection every 8 weeks. Sixteen (of 38, 42.1%) patients required dose escalation, to every 4 weeks (N = 15 of these 16, 93.8%) or every 6 weeks (N = 1 of 16, 6.3%); of the 16 patients, 6 (of 16, 37.5%) required a single re-induction dose, of either 390mg (N = 4 of 16, 25.0%) or 260mg (N = 2 of 16, 12.5%), or two re-induction doses of 390mg (N = 1 of 16, 6.3%); the remaining 9 patients did not require any re-induction doses. Alternatively, 2 (of 38, 5.3%) patients had either a single re-induction dose of 520mg, or two re-induction doses of 390mg without escalation of dosing frequency. Of the 18 total patients that required dose escalation, re-induction, or both, 13 (of 18, 72.2%) had available UST levels drawn a median of 11.6 months [IQR: 2.3–14.8]

after induction date, with a median of 6.2 ug/mL [IQR: 3.9–7.7]. Of the 20 patients who did not require any dose adjustment after initiating maintenance, only 6 (of 20, 30.0%) patients had available UST levels drawn a median of 2.9 months [IQR: 2.1–12.1] after induction date, with a median level of 5.9 ug/mL [IQR: 4.1–6.6]. None of the total 19 patients who had available UST levels had any antibodies to UST. Median duration from time of CD diagnosis to UST induction dose was 3.5 years [IQR: 1.6–5.9]; median duration of UST treatment was 62.1 weeks [IQR: 31.3–81.7]. At the time of last follow-up, 32 (of the total 38, 84.2%) patients remained on UST, and 11 (of the total 38, 28.9%) patients were also taking oral corticosteroids.

Outcome Measures

The median aPCDAI decreased from 20.0 [IQR: 10.0–30.0] at time of first dose to 5.0 [IQR: 0.0–15.0] at time of last dose (p = 0.0003) (Table 3). Following induction, 7 (18.4%) patients were in clinical remission per aPCDAI, compared with 23 (60.5%) at last dose (p = 0.0001). In parallel, median serum albumin levels improved from 3.8 g/dL [IQR: 3.4–4.2] to 4.1 g/dL [IQR: 3.5–4.5] (p = 0.001), and median hematocrit increased from 37.4% [IQR: 35.0–41.6] to 40.8% [IQR: 37.0–44.0] (p = 0.0001) (Table 3). Median CRP decreased from 4.4 mg/L [IQR: 0.9–12.0] to 3.6 mg/L [IQR: 0.8–9.0] (p = 0.38) (Table 3). A similar but non-significant trend towards improvement was seen in BMI Z-scores from −0.2 [IQR: −0.71 to −0.31] to −0.04 [IQR: −0.49 to 0.4] (p = 0.313) (Table 3). No significant changes were noted in height and weight Z-scores. At the time of last follow-up, 32 (84.2%) patients remained on UST, including 15 (of 18, 83.3%) patients who required escalation, re-induction, or both of UST. Two (of the 38, 5.3%) patients were forced to discontinue UST due to insurance issues, 1 (of the 38, 2.6%) patient chose to discontinue all IBD treatment, and 5 (of the 38, 13.2%) patients stopped due to secondary loss of response.

Among the 18 patients who dose escalated, received re-induction, or both, the median aPCDAI decreased from 25.0 [IQR: 10.0–30.0] to 5.0 [IQR: 5.0–15.0] (p = 0.005) (Table 4). At induction, 2 (of the 18, 11.1%) were in clinical remission by aPCDAI, compared with 11 (of the 18, 61.1%) at last dose, all of which would have followed UST dose adjustments (p = 0.004). Median hematocrit improved from 35.4% [IQR: 31.6–40.0] to 40.4% [IQR: 36.0–44.0] (p = 0.0007) (Table 4). No significant changes were seen in albumin, CRP, or Z scores for BMI (Table 4).

Among the 13 patients with perianal disease, aPCDAI decreased from 20.0 [IQR: 10.0–30.0] to 5.0 [IQR: 0.0–15.0] (p = 0.003) (Table 5). Median hematocrit improved from 36.1% [IQR: 33.3–38.0] to 40.4% [IQR: 36.0–45.0] (p = 0.02) (Table 5). At induction, none of these 13 patients were in clinical remission by aPCDAI, compared with 5 (of the 13, 38.5%) at last dose (p-value could not be calculated). No significant changes were seen in albumin, CRP, or Z scores for BMI (Table 5).

In terms of the course of CD while on UST, in total, 10 (26.3%) patients experienced at least one CD flare while on UST, with 5 (13.2%) patients requiring inpatient admission. Eleven (28.9%) patients underwent surgery for CD prior to first dose of UST, while only 1 (2.6%) patient with no prior surgical history had surgery after starting UST to resect a pre-existing ileal stricture. Of note, neither of the two patients who were forced to discontinue due to

insurance issues had any CD flares or inpatient admissions related to worsening CD during the period of this study.

Adverse Events

Thirty-four (of the total 38, 89.5%) patients had no adverse events since the first dose of UST. One (2.6%) patient had a suspected anaphylactic reaction to an intravenous re-induction dose but tolerated subsequent subcutaneous doses in a monitored clinical setting. Three (7.9%) patients were diagnosed with infections while on UST, including a staphylococcus skin infection, and a mycobacterium avium complex (MAC) pulmonary infection diagnosed from cultures drawn only one day after starting UST and treated with outpatient antibiotics. One (2.6%) patient required hospitalization for parenteral antibiotics to treat a bacterial super-infection of their refractory psoriasis. Given the efficacy of UST at treating their CD, all of these particular patients were continued on the medication.

Discussion

This retrospective cohort study highlights the efficacy of UST in treating pediatric patients with CD refractory to other biologic therapies. Our cohort captured the phenotypic heterogeneity of pediatric patients with CD, including stricturing and penetrating disease, growth failure, perianal disease, and patients with surgical histories. Despite the complexity and severity of disease, patients experienced significant clinical and biomarker improvement. Eighty-four percent of patients remained on UST at the time of last follow-up, and 61% achieved clinical remission by aPCDAI. Our findings are similar to those documented in limited pediatric literature. A similar-sized retrospective cohort study by Dayan *et al.* (2019) reported a 50% clinical remission rate in biologic-exposed pediatric patients, with 75% of patients remaining on UST at 1-year follow-up (8). However, the two cohorts differ in that our study included a higher percentage of patients with an IBD-related surgical history, growth failure, and stricturing and/or penetrating disease.

Our findings also align with a pediatric study by Chavannes *et al.* (2019) that demonstrated a significant decrease in aPCDAI, and a 40% clinical remission rate at one-year (7). These investigators also highlighted a significant improvement in BMI Z-scores for patients whose height or weight Z-scores had previously down-trended by a major percentile line on the World Health Organization growth chart. We opted to define our growth failure cohort in concert with the Paris classification, which only accounts for reductions in height velocity. In our overall population, we document improvement in BMI Z-scores, which may have attained statistical significance with a larger cohort or additional follow-up time.

Compared with reports of adults with CD, we found similar response rates, but with a higher percentage of patients remaining on UST through follow-up, likely due to less FDA-approved therapeutic options in the pediatric population relative to the adult population. In a large multi-center retrospective cohort study, Wils *et al.* (2016) showed 68% of patients continued UST at a 1-year follow up, with 65% demonstrating clinical response within 3 months (13). Similarly, Ma *et al.* (2017) demonstrated a clinical response rate of 60% with a remission rate of 25% within 24 weeks of starting UST (14).

We further analyzed the subpopulation of patients who required a more aggressive UST regimen in order to describe any effects on overall efficacy. Decisions to re-induce or alter the frequency of dosing were made at the discretion of the patient's primary pediatric gastroenterologist. Among patients who required escalations in therapy, 83.3% remained on UST through follow-up. While 61.1% of this sub-cohort achieved clinical remission at time of last UST dose, these patients were likely sicker as evidenced by a smaller percentage of this sub-cohort already in clinical remission compared with our overall patient cohort (11.1% vs 18.4%) or compared with our sub-cohort of patients who did not require dose adjustment (25.0%). Additionally, the median aPCDAI was higher (25.0 vs 20.0) for both the overall cohort and for the sub-cohort not requiring dose adjustment at the time of their induction dose. Notably, a significant increased percentage eventually reached clinical remission after dose adjustment compared with only their induction UST dose, which differs from findings of a previous pediatric trial that showed no association between dose escalation and clinical remission (8).

We further analyzed the patients with perianal disease, which, similar to patients requiring dose adjustments, likely represents a sicker sub-cohort of patients. This was evidenced by none of this subset of patients being in clinical remission at the time of induction. However, 38.5% reached clinical remission by aPCDAI at time of last UST dose.

While we acknowledge our study is limited by its small size, it is still comparable to the available published data from pediatric studies. We found no significant rates of adverse events, both within our total cohort and when analyzing our sub-cohort of patients who required re-induction or increased dosing frequency, consistent with multiple adult cohort studies (15–18). No patient experienced a severe infection that necessitated discontinuation of UST, although we acknowledge that one patient with a history of multiple infections of known refractory psoriasis required parenteral antibiotics to treat a superimposed bacterial infection. Similar psoriasis exacerbations have been documented in pediatric and adult reports (7, 15, 16). Additionally, it is unlikely that our patient's MAC infection was associated with UST, as the patient had known pulmonary nodules prior to induction, and the culture that eventually speciated to MAC was drawn one day following the initial UST induction dose. In sum, our data suggest that increasing the dosing frequency or re-inducing with UST is efficacious in the pediatric population, and is not associated with significantly increased adverse events.

Although our study presents a similar number of patients to the largest published pediatric cohorts in the published literature (7–8), the overall sample size is still relatively small, highlighting the need for additional and better controlled studies. Our study's retrospective design poses limitations, and larger prospective blinded randomized control trials are crucial to further elucidate UST's generalizable efficacy and safety in pediatric patients with CD. We did not routinely obtain serum drug levels, given the lack of standardized pediatric guidelines. Adult data show improved biomarker and endoscopic response when targeting trough drug levels above 4.5 μg/mL (17), and future pediatric research may focus on development of target goals to optimize patient outcomes. In a sub-study of the UNITI trial, researchers noted decreases in the Simplified Endoscopic Score for Crohn's Disease (SES-CD) in almost 50% of patients, indicating that UST is associated with mucosal healing

(18). As histologic remission becomes the ultimate target of IBD therapy (19), it will be essential to include endoscopic data in future pediatric trials. We did not include analysis of fecal calprotectin levels as this was not consistently available and this was a retrospective study.

Our findings suggest that, among our small cohort, UST is effective as a non-surgical option for pediatric patients with refractory CD. No significant safety concerns were observed in our patients. The medication was well-tolerated, even in the subset of patients who required dose adjustments to achieve clinical benefit, and in patients with perianal disease. As treatment options continue to expand in pediatric patients with IBD, UST provides an alternative biologic to treat inflammation, either alone or possibly in combination with other new therapeutic agents. If possible, conducting larger, prospective, controlled and randomized clinical trials is crucial to establish thorough safety and efficacy data, as with parallel adult trials. Future predictive modeling may be needed to further individualize therapy and select patients best suited for IL-12/23 blockage versus conventional first-line anti-TNF therapy.

Acknowledgments

Abbreviations:

UST	ustekinumab
IL	interleukin
CD	Crohn's disease
aPCDAI	abbreviated pediatric CD activity index
TNF	tumor necrosis factor
UC	ulcerative colitis
IBD-U	inflammatory bowel disease unclassified
IV	intravenous
Hct	hematocrit
CRP	C-reactive protein
Alb	albumin
BMI	body mass index

IQR	interquartile range
MAC	mycobacterium avium complex
PSC	primary sclerosing cholangitis
IMM	immunomodulator

References

1. Lamb YN, Duggan ST. Ustekinumab: A Review in Moderate to Severe Crohn's Disease. Drugs 2017; 77:1105–1114. 10.1007/s40265-017-0765-6 [PubMed: 28528528]

2. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. New England Journal of Medicine 2016; 375:1946–1960. 10.1056/NEJMoa1602773

3. Sandborn WJ, Gasink C, Gao L-L, et al. Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease. New England Journal of Medicine 2012; 367:1519–1528. 10.1056/NEJMoa1203572

4. Rinawi F, Rosenbach Y, Assa A, et al. Ustekinumab for Resistant Pediatric Crohn Disease. Journal of Pediatric Gastroenterology and Nutrition 2016; 62:e34. 10.1097/MPG.0000000000000503 [PubMed: 25023579]

5. Bishop C, Simon H, Suskind D, et al. Ustekinumab in Pediatric Crohn Disease Patients. Journal of Pediatric Gastroenterology and Nutrition 2016; 63:348–351. 10.1097/MPG.0000000000001146 [PubMed: 26854655]

6. Cameron FL, Garrick V, Russell RK. Ustekinumab in Treatment of Refractory Paediatric Crohn Disease. Journal of Pediatric Gastroenterology and Nutrition 2016; 62:e30. 10.1097/MPG.0000000000000608

7. Chavannes M, Martinez-Vinson C, Hart L, et al. Management of Paediatric Patients With Medically Refractory Crohn's Disease Using Ustekinumab: A Multi-Centred Cohort Study. J Crohns Colitis 2019; 13:578–584. 10.1093/ecco-jcc/jjy206 [PubMed: 30541021]

8. Dayan JR, Dolinger M, Benkov K, et al. Real World Experience With Ustekinumab in Children and Young Adults at a Tertiary Care Pediatric Inflammatory Bowel Disease Center. J Pediatr Gastroenterol Nutr 2019; 69:61–67. 10.1097/MPG.0000000000002362 [PubMed: 31058718]

9. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011; 17:1314–1321. 10.1002/ibd.21493 [PubMed: 21560194]

10. Janssen Immunology. Dosing and Administration Guide for Stelara in Crohn's Disease. Janssen Carepath. https://www.janssencarepath.com/sites/www.janssencarepath.com/files/stelara-dosing-and-administration-guide.pdf. Accessed October 14, 2020

11. Turner D, Griffiths AM, Walters TD, et al. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. Inflamm Bowel Dis 2012; 18:55–62. 10.1002/ibd.21649 [PubMed: 21351206]

12. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377–381. 10.1016/j.jbi.2008.08.010 [PubMed: 18929686]

13. Wils P, Bouhnik Y, Michetti P, et al. Subcutaneous Ustekinumab Provides Clinical Benefit for Two-Thirds of Patients With Crohn's Disease Refractory to Anti-Tumor Necrosis Factor Agents. Clin Gastroenterol Hepatol 2016; 14:242–250.e1–2. 10.1016/j.cgh.2015.09.018 [PubMed: 26432476]

14. Ma C, Fedorak RN, Kaplan GG, et al. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. Alimentary Pharmacology & Therapeutics 2017; 45:1232–1243. 10.1111/apt.14016 [PubMed: 28252210]

15. Hay R a. S, Pan JY. Paradoxical flare of pustular psoriasis triggered by ustekinumab, which responded to adalimumab therapy. Clin Exp Dermatol 2014; 39:751–752. 10.1111/ced.12392 [PubMed: 24984757]

16. Caca-Biljanovska N, V'lckova-Laskoska M, Laskoski D. Successful management of ustekinumab-induced pustular psoriasis without therapy discontinuation. Acta Dermatovenerol Croat 2013; 21:202–204. [PubMed: 24183227]

17. Battat R, Kopylov U, Bessissow T, et al. Association Between Ustekinumab Trough Concentrations and Clinical, Biomarker, and Endoscopic Outcomes in Patients With Crohn's Disease. Clin Gastroenterol Hepatol 2017; 15:1427–1434.e2. 10.1016/j.cgh.2017.03.032 [PubMed: 28365485]

18. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease. Gastroenterology 2018; 155:1045–1058. 10.1053/j.gastro.2018.06.035 [PubMed: 29909019]

19. Bryant RV, Winer S, Travis SPL, et al. Systematic review: histological remission in inflammatory bowel disease. Is "complete" remission the new treatment paradigm? An IOIBD initiative. J Crohns Colitis 2014; 8:1582–1597. 10.1016/j.crohns.2014.08.011 [PubMed: 25267173]

What is known:

- Ustekinumab (UST) is a monoclonal antibody against IL-12/23, approved to treat adult patients with psoriasis or Crohn's disease (CD).

- Limited data report on the efficacy and safety of UST in pediatric patients with medically refractory CD.

What is new:

- In our patients, greater than 60% of pediatric patients with CD achieved clinical remission after median 62 weeks on UST.

- Pediatric patients with CD who required UST dose adjustment had significant improvement in abbreviated pediatric CD activity index (aPCDAI).

- Pediatric patients with perianal CD had improvement in aPCDAI.

- No significant adverse events were reported in most of our pediatric patients with CD after starting UST.

Table 1:

Patient demographics and clinical characteristics

	CD, N = 38
Biological male sex, No. (%) (including one gender non-binary)	24 (63.2%)
Age at diagnosis, median [IQR] years	12.5 [10.2 – 15.0]
Duration of disease prior to starting UST, median [IQR] years	3.5 [1.6 – 5.9]
Age at UST initiation, median [IQR] years	17.2 [14.5 – 18.8]
Duration of UST, median [IQR] months	14.3 [7.2 – 18.8]
Paris classification: disease location, No. (%)	
Lower disease	38 (100%)
Distal 1/3 ileum +/− limited cecal disease (L1)	6 (15.8%)
Colonic (L2)	5 (13.2%)
Ileocolonic (L3)	27 (71.1%)
Perianal disease	13 (34.2%)
Upper disease	18 (47.4%)
Proximal to ligament of Treitz (L4a)	7 (18.4%)
Distal to ligament of Treitz and proximal to distal 1/3 ileum (L4b)	11 (28.9%)
L4a + L4b	0 (0.0%)
Paris classification: disease behavior, No. (%)	
Non-stricturing, non-penetrating (B1)	26 (68.4%)
Stricturing (B2)	7 (18.4%)
Penetrating (B3)	4 (10.5%)
B2B3	2 (5.3%)
Growth delay [*], No. (%)	7 (18.4%)
Any prior surgery, No. (%)	11 (28.9%)
Comorbidities, No. (%)	
Arthritis	3 (7.9%)
PSC	2 (5.3%)
Erythema nodosum	1 (2.6%)
Genital ulcers	3 (7.9%)
Oral ulcers	5 (13.2%)
Other (e.g. psoriasis, uveitis, ileal perforation, vulvar edema)	14 (36.8%)

[*] Growth delay defined as a reduction in absolute height z-score at any time since diagnosis of 0.75 points, per Paris classification (9)

Abbreviations: IQR, interquartile range; PSC, primary sclerosing cholangitis; UST, ustekinumab

Table 2:

Prior medications (N = 38)

Prior anti-TNF agent [†], No. (%)	
1 anti-TNF agent	25 (65.8%)
2 or 3 anti-TNF agents	13 (34.2%)
Prior IMM[‡], No. (%)	
1 IMM	17 (44.7%)
2 or 3 IMM	12 (31.6%)
Prior vedolizumab, No. (%)	5 (13.2%)
On steroids at UST start, No. (%)	7 (18.4%)

[†]Anti-TNF agents include: infliximab, adalimumab, certolizumab

[‡]IMM include: azathioprine, mercaptopurine, methotrexate

Abbreviations: TNF, tumor necrosis factor; UST, ustekinumab; IMM, immunomodulator

Table 3:

Changes in clinical disease activity, biomarkers, and growth outcomes in overall cohort (N = 38)

	At UST induction (median) [IQR]	At last follow-up (median) [IQR]	p-value
aPCDAI	20.0 [10.0–30.0]	5.0 [0.0–15.0]	0.003
In clinical remission (aPCDAI <10) (No, %)	7 (18.4%)	23 (60.5%)	0.0001
Albumin (g/dL)	3.8 [3.4–4.2]	4.1 [3.5–4.5]	0.001
Hematocrit (%)	37.4 [35.0–41.6]	40.8 [37.0–44.0]	0.0001
C-reactive protein (mg/L)	4.4 [0.9–12.0]	3.6 [0.8–9.0]	0.38
Body Mass Index (Z-score)	−0.2 [−0.71 to −0.31	−0.04 [−0.49 to 0.4]	0.31

Abbreviations: aPCDAI, abbreviated pediatric CD activity index; IQR, interquartile range; UST, ustekinumab

Table 4:

Changes in clinical disease activity, biomarkers, and growth outcomes in patients requiring UST dose adjustment (N = 18)

	At UST induction (median) [IQR]	At last follow-up (median) [IQR]	p-value
aPCDAI	25.0 [10.0–30.0]	5.0 [5.0–15.0]	0.005
In clinical remission (aPCDAI <10) (No, %)	2 (11.1%)	11 (61.1%)	0.004
Albumin (g/dL)	3.6 [3.0–4.0]	3.8 [3.2–4.2]	0.07
Hematocrit (%)	35.4 [31.6–40.0]	40.4 [36.0–44.0]	0.0007
C-reactive protein (mg/L)	7.3 [1.3–17.6]	3.8 [1.0–12.8]	0.48
Body Mass Index (Z-score)	0.07 [−0.42 to 0.34]	−0.22 [−1.08 to 0.8]	0.61

Abbreviations: aPCDAI, abbreviated pediatric CD activity index; IQR, interquartile range; UST, ustekinumab

Table 5:

Changes in clinical disease activity, biomarkers, and growth outcomes in patients with perianal disease (N = 13)

	At UST induction (median) [IQR]	At last follow-up (median) [IQR]	p-value
aPCDAI	25.0 [10.0–35.0]	10.0 [5.0–20.0]	0.037
In clinical remission (aPCDAI <10) (No, %)	0 (0.0%)	5 (38.5%)	N/A
Albumin (g/dL)	3.6 [3.3–4.1]	4.2 [3.2–4.2]	0.11
Hematocrit (%)	36.1 [33.3–38.0]	40.4 [36.0–45.0]	0.02
C-reactive protein (mg/L)	7.3 [1.1–10.2]	6.0 [1.0–15.0]	0.34
Body Mass Index (Z-score)	0.07 [−0.98 to 0.87]	0.37 [−1.14 to 1.18]	0.92

Abbreviations: aPCDAI, abbreviated pediatric CD activity index; IQR, interquartile range; UST, ustekinumab