Augmented ustekinumab dosing is needed to achieve clinical response in patients with anti-TNF refractory pediatric Crohn's disease: a retrospective chart review

Phinga Do¹, John Andersen¹,², Ashish Patel¹,², Gaith Semrin¹,², Luis Sifuentes-Dominguez¹,², Phuong Luu¹, Bhaskar Gurram¹,²

¹Department of Pediatrics, Children's Health Medical Center Dallas, Dallas, TX, 75235, USA
²Department of Pediatric Gastroenterology, UT Southwestern Medical Center, Dallas, TX, 75235, USA

Abstract

Background: Ustekinumab is a monoclonal antibody that inhibits interleukins 12 and 23. It is approved for treatment of Crohn's disease (CD) in adults; however, there is a paucity of data regarding its use in pediatric CD. We describe our experience using ustekinumab in anti-TNF refractory CD pediatric patients.

Methods: We performed a retrospective chart review on pediatric patients with CD who were started on ustekinumab from January 2016 to November 2018. We collected patient's clinical history, previous treatment history, surgeries related to CD, disease severity, as measured by abbrPCDAI, and endoscopic severity as recorded by SES-CD before and after ustekinumab.

Results: We identified 10 patients with CD who were started on ustekinumab due to non-response to currently approved agents. Seven patients needed augmented maintenance dosing every 4-6 weeks to achieve clinical response or remission. Six of these seven patients had therapeutic drug monitoring during the course of treatment, with five patients showing subtherapeutic drug levels of <4.5 μg/mL while on standard maintenance dosing every 8 weeks, and four patients showing therapeutic drug levels of >4.5 μg/mL on augmented dosing interval. The remaining three patients were on standard maintenance dosing for the duration of treatment.

Conclusion: In this retrospective chart review, 7 out of 10 patients with anti-TNF refractory pediatric-onset CD required augmented maintenance doses of ustekinumab to achieve clinical response or remission. A prospective study is needed to define appropriate ustekinumab dosing and interval in management of pediatric CD.
Keywords
Ustekinumab, Pediatric Crohn's disease, anti-TNF-refractory Crohn's disease, Inflammatory bowel disease, Therapeutic drug monitoring, Clinical response
Introduction
Together, ulcerative colitis and Crohn’s disease (CD) make up inflammatory bowel disease (IBD), an autoimmune-mediated process of unclear etiology. The global incidence of pediatric IBD has been rising rapidly, with the highest incidence of CD being in Europe at 23/100000 person years and North America at 15.2/100000 person years\(^1\). Earlier onset of IBD is associated with higher impact on growth and development, more aggressive disease course, and increased need for immunomodulators\(^2\). Anti-tumor necrosis factors (anti-TNFs) form the forefront of management of patients with CD who do not respond to steroids and immunomodulatory medications\(^3\).

Among pediatric patients with CD who are started on anti-TNF treatments, about 10–25% do not respond to it (primary non-responders)\(^4\). Of those who initially respond, loss of response and adverse effects limit duration of therapy. At 1, 3, and 5 years after therapy initiation, the probability of patients remaining on infliximab is only 0.87, 0.74, and 0.67, respectively (secondary non-responders)\(^5\). Thus, there is a significant need for novel therapies for management of CD.

Among the newer biologics approved for treatment of CD is ustekinumab, a human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity to the p40 subunit of human interleukin (IL)-12 and IL23. Ustekinumab prevents IL12 and IL23 bioactivity by preventing their interaction with their cell surface receptor protein IL12Rβ1. Through this mechanism of action, ustekinumab effectively neutralizes IL12 (Th1)- and IL23 (Th17)-mediated cellular responses. It has recently been approved for the treatment of moderate to severe active CD in adults\(^6\). However, data on usage of ustekinumab in management of pediatric Crohn’s disease is limited to small case series\(^7\). Here we describe our experience on using ustekinumab for management of TNF-refractory pediatric CD.

Methods
We performed a retrospective chart review on 10 pediatric CD patients who failed anti-TNF therapy and were treated with ustekinumab between January 2016 and November 2018. Ustekinumab levels and antibodies were done either by Miraca or Inform Diagnostics. Both these labs used automated enzyme linked immunosorbent assay (ELISA) assay for simultaneous antibody and drug levels.

This study was approved by the Institutional Review Board (IRB) of Dallas Children’s Hospital (study #25338). Request for waiver of patient/guardian consent for this study was approved by the IRB.

Data collection
We collected baseline demographic data, disease phenotype based on Paris Classification\(^8\), disease related complications, previous treatment history, and reason for changing therapy.

To assess clinical response to ustekinumab, we calculated the Abbreviated Pediatric Crohn’s Disease Activity Index (abbrPCDAI) prior to starting therapy, 2–3 months after therapy initiation, and at the last office visit before conclusion of the study\(^9\). When no office visits were available immediately prior to treatment initiation, telephone and email encounters were used to assess patients’ clinical symptoms to calculate abbrPCDAI. Where possible we also calculated the Simple Endoscopic Score for Crohn’s Disease (SES-CD) before and after treatment initiation\(^10\). Body Mass Index (BMI) before and after treatment was collected.

Laboratory measurements, which include hematocrit, C-reactive protein (CRP), and albumin, were also collected before and after treatment initiation. We also looked at the trough ustekinumab levels where available in relation to dose and response to therapy.

Data analysis
Patients are categorized as anti-TNF primary non-responders if there’s no clinical response during therapy induction, and secondary non-responders if there’s loss of response during maintenance phase\(^11\). Based on abbrPCDAI, clinical response is defined as ≥15 points reduction, and clinical remission is defined as <10. We define sustained clinical remission as abbrPCDAI of <10 with no subsequent elevation in AbbrPCDAI as of the last visit. Disease severity is categorized as follows: severe >25; moderate 16–25; mild <16. We use the following SES-CD cutoff to define disease severity: remission 0–2; mild 3–6; moderate 7–15; and severe >16\(^11\). Endoscopic response is defined as ≥50% decrease in SES-CD score compared to baseline\(^12\). Based on previous studies we used a target ustekinumab trough level of >4.5 µg/mL\(^13\).
ranged from 9 to 19 years (median age of 14.5 years). Duration of disease ranged from 3 to 14 years (median duration of 6.5 years). Table 1 summarizes patients’ demographic, disease phenotype at diagnosis, extraintestinal manifestations, disease related surgeries, treatment history, and reasons for changing therapy to ustekinumab. Of note, patient one was diagnosed at two years of age, putting him in the very early onset IBD (VEO-IBD) category. Even though VEO-IBD is a phenotypically distinct group, there’s still significant overlap in behavior and response to therapy between VEO-IBD and conventional-onset IBD. All 10 patients in our cohort were refractory to anti-TNF therapy.

Table 2 summarizes the ustekinumab induction and maintenance dose used in these patients. For induction, the dosing varied among patients with 7 out of 10 receiving induction doses per current recommendations. The remaining 3 patients received doses as described in Table 2.

Patients on augmented dose
Of the seven patients who received augmented maintenance doses, all seven showed clinical response, as shown in Figure 1 (patients 1–7), and all but one patient achieved sustained clinical remission as assessed by abbrPCDAI. One patient (patient 7) achieved remission after 5 months of specific carbohydrate diet (SCD) and ustekinumab at Q8 maintenance. He remained in remission for the next 17 months, then developed fatigue and bloody stool when diet was liberalized. His symptoms did not respond to reintroduction of SCD. However, he went into clinical remission when ustekinumab maintenance interval was changed to Q6 weeks.

Only 4 out of 10 patients had endoscopy before and after ustekinumab treatment. Of these, three patients showed endoscopic response and one showed worsening of SES-CD score (Figure 1C). Of note, all 3 patients who showed endoscopic response received augmented dose. While no patient showed mucosal remission, mucosal inflammation did improve from severe to mild, severe to moderate, and moderate to mild in three patients.

Laboratory indices also improved in 6 out of 7 patients (Table 3). The most significant and consistent improvements were seen in CRP and albumin (Figure 2C–F). BMI improved significantly in patients with pre-treatment BMI below the 25th percentile. In patients with normal BMI (5th to 85th percentile), the BMI either decreased or showed small numerical improvement (Figure 2G,H).

Among the seven patients, five had ustekinumab trough level showing low or undetectable drug level when receiving medication at a 6 or 8 week intervals (Table 2). Subsequently, four patients had escalation in frequency to Q4 and either achieved remission or clinical improvement. Following this change in interval, repeat drug levels for three patients were all therapeutic at 8, 7.1, and >10 µg/mL. Subsequently one of these three patients’ maintenance interval was decreased to Q6, and by the time of this study’s conclusion, a repeat level has not been obtained. Frequency was increased to Q6 in another patient, resulting in clinical remission. One of the patients was empirically started on a maintenance dose of Q4 interval and had trough levels of >10 µg/mL at 4 weeks. Frequency was subsequently changed to Q8, but a repeat drug level was not obtained (Table 2).

Patients on standard dose interval
Three of the 10 patients were on standard ustekinumab dosing. One patient had symptomatic duodenal stricture and obstruction, resulting in abdominal pain, vomiting, and weight loss. He underwent endoscopic stricture dilation 2 months prior to initiation of ustekinumab. After ustekinumab was started, he required two subsequent dilations in a 2-month period, but had subsequently been in remission for the next 5 months on high dose steroid. However, this was confounded by his family continuing 60mg prednisone daily for at least 4 months (2 months longer than prescribed). Unfortunately, there was no subsequent follow ups as he had transitioned to adult care. His hematocrit, CRP, and albumin all improved compared to levels prior to ustekinumab, while his BMI decreased slightly. The remaining two patients had disease worsening on ustekinumab, shown by serology and worsening abbrPCDAI. None of these three patients had their levels checked.

Complications observed while on ustekinumab included infusion reactions, such as low-grade fever, joint pain and vomiting within one week of infusion, and infections such as *Clostridium difficile*, influenza, and pneumonia. Of note, one patient developed perianal abscess within a few weeks of the first ustekinumab induction, requiring hospitalization and resulting in stopping therapy. Upon the second induction more than 1.5 years later, he again developed forearm abscess requiring hospitalization. However, his CD went into remission with ustekinumab. Work-up for immune deficiency was negative. He was later diagnosed with maturity-onset diabetes of the young.

Discussion
Here we report 10 pediatric patients with CD refractory to currently approved medications including anti-TNFs, immunomodulators and some to vedolizumab, with seven showing a clinical response to ustekinumab treatment. The majority of our patients showed positive response to ustekinumab within the first 2–3 months of therapy and clinical remission by the end of this study was concluded. Four of these seven patients had endoscopic data pre- and post-ustekinumab, out of which three showed an improvement as measured by SES-CD. In general, SES-CD score showed higher level of disease activity than abbrPCDAI, which is likely due to poor correlation between these two indices. Moreover, abbrPCDAI and SES-CD information were collected at different times in the treatment course, resulting in small differences in disease activities. CRP, albumin, and BMI showed the largest improvement, and hematocrit improved in all but two patients who responded to treatment.

To achieve clinical response and/or remission, 7 out of 10 patients needed augmented maintenance doses. Of note, one patient’s (patient 7) level of 1.1 µg/mL coincided with...
| Patient | Gender | Age at diagnosis | Current age | Age at ustekinumab initiation | Paris Classification at diagnosis | abbrPCDAI at diagnosis | Extra-intestinal manifestations | Perianal disease | Surgery | Past immunomodulators | Past anti-TNF therapy | Other past biologics | Reason for switching to ustekinumab |
|---------|--------|------------------|-------------|-----------------------------|----------------------------------|------------------------|-------------------------------|----------------|---------|-----------------|-----------------|-----------------|----------------------------------|
| 1       | M      | 2                | 11          | 9                           | A1aL3L4aB1pG1                    | 30                     | None                          | Yes            | Ileocectomy with ileostomy | Thiopurines     | Infliximab, adalimumab | NA                              |
| 2       | M      | 13               | 16          | 15                          | A1bL3L4aB1G1                    | 40                     | None                          | No             | No                  | Methotrexate     | Infliximab, adalimumab | Vedolizumab                        |
| 3       | F      | 10               | 18          | 17                          | NA                              | NA                     | Arthritis                      | No             | Complete colectomy | Thiopurines, methotrexate | Infliximab, adalimumab | NA                           |
| 4       | F      | 9                | 16          | 14                          | A1aL3L4aB1G1                    | 30                     | None                          | No             | Distal loop ileostomy | Thiopurines, methotrexate | Infliximab, adalimumab | Vedolizumab                        |
| 5       | F      | 9                | 13          | 11                          | A1aL3aB1pG1                     | 35                     | None                          | Yes            | No                  | Methotrexate     | Infliximab, adalimumab | Vedolizumab                        |
| 6       | M      | 11               | 17          | 14                          | A1bL1L4aB1G1                    | 25                     | Arthritis                      | Yes            | No                  | Thiopurines, methotrexate | Infliximab, adalimumab, certolizumab | NA                           |
| 7       | M      | 9                | 15          | 12                          | A1aL3L4aB1pG1                    | 30                     | Fever, arthritis, episcleritis | Yes            | No                  | NA              | Infliximab, adalimumab | NA                              |
| 8       | M      | 14               | 19          | 17                          | A1bL3L4aB2G1                    | 20                     | None                          | No             | No                  | Thiopurines     | Adalimumab       | NA                              |
| 9       | F      | 7                | 21          | 19                          | A1aL3B1P                         | 35                     | Arthritis, fever               | Yes            | No                  | Thiopurines, methotrexate | Infliximab, adalimumab | NA                           |
| 10      | F      | 10               | 18          | 16                          | A1bL3L4aB2G1                    | 45                     | Arthritis, fever               | Yes            | No                  | Thiopurines, methotrexate | Infliximab, adalimumab | Vedolizumab                        |

EIM - extra intestinal manifestations. AbbrPCDAI - abbreviated pediatric Crohn Disease activity index.
Figure 1. Clinical and endoscopic response. Abbreviated-pediatric Crohn’s disease activity index in patients with (A) augmented ustekinumab dosing and (B) Q8 dosing. (C) simple endoscopic score-Crohn’s disease (SES-CD) pre and post-ustekinumab initiation.

Table 2. Ustekinumab dosing, interval, levels, duration of therapy, and complications.

| Patient | Induction (mg) | Maintenance (mg) | Initial interval (weeks) | Trough level (µg/ml) | Final maintenance dose (mg) | Final intervals (weeks) | Last trough level (µg/ml) | Therapy duration (weeks) | Complications on Ustekinumab |
|---------|----------------|------------------|--------------------------|----------------------|-----------------------------|------------------------|--------------------------|--------------------------|-----------------------------|
| 1       | 45x2           | 45               | 8                        | NA                   | 90                          | 8                      | NA                       | 142                      | NA                          |
| 2       | 520            | 90               | 8                        | undetectable         | 90                          | 4                      | NA                       | 59                       | NA                          |
| 3       | 260            | 90               | 8                        | 3.6                  | 90                          | 4                      | 8                        | 63                       | infusion reaction           |
| 4       | 240            | 90               | 6                        | 0.8                  | 90                          | 4                      | 7.1                      | 71                       | NA                          |
| 5       | 180            | 45x1, then 90    | 6                        | 0.1                  | 90                          | 6                      | >10                      | 73                       | NA                          |
| 6*      | 390            | 90               | 4                        | 10                   | 90                          | 8                      | NA                       | 16                       | skin abscess                |
| 7       | 90x3 Q4        | 90               | 8                        | 1.1                  | 90                          | 6                      | NA                       | 143                      | skin abscess                |
| 8       | 260            | 90               | 8                        | NA                   | 90                          | 8                      | NA                       | 55                       | Clostridium difficile infection |
| 9       | 390            | 90               | 8                        | NA                   | 90                          | 8                      | NA                       | 36                       | NA                          |
| 10      | 390            | 90               | 8                        | NA                   | 90                          | 8                      | NA                       | 25                       | NA                          |

*This patient was exposed to ustekinumab 2 years prior for a duration of 4 weeks.
### Table 3. Laboratory and clinical response to ustekinumab.

| Patient | Hematocrit Before | Last Hematocrit | CRP (mg/dl) before | Last CRP (mg/dl) | Albumin Before | Last Albumin | BMI % before | Last BMI % | abbrPCDAI pre tx | abbrPCDAI 2-3 months on tx | abbrPCDAI last assessment | pre tx SES-CD | post Tx SES-CD |
|---------|-------------------|-----------------|--------------------|-----------------|----------------|--------------|--------------|------------|-------------|---------------------|-----------------------------|--------------------------|-------------|-------------|
| 1       | 37.4              | 38              | 10.3               | <0.29           | 3.4            | 3.7          | 63           | 60         | 35          | 5                   |                             | 0                        | NA          | NA          |
| 2       | 41.6              | 43              | 0.869              | 0.516           | 3.2            | 3.8          | 99           | 99.3       | 20          | 5                   |                             | 0                        | NA          | NA          |
| 3       | 32                | 36              | 5.61               | <0.29           | 2.7            | 3.3          | 1.31         | 38.9       | 30          | 15                  | NA                          | 10                       | 12          |             |
| 4       | 28.1              | 38.2            | 5.06               | <0.29           | 2.2            | 4            | 0.15         | 65         | 40          | 30                  | 5                           | 0                        | 20          | 5           |
| 5       | 35.3              | 35              | 9.91               | 1.92            | 2.6            | 3.1          | 1.88         | 42.3       | 35          | 15                  | 0                           | 36                       | 8           |             |
| 6*      | 40.6              | 40.6            | 0.52               | 0.43            | 3.3            | 4            | 79.8         | 77.8       | 15          | 0                   | NA                          | 14                       | 5           |             |
| 7       | 39.1              | 37              | 1.39               | 1.1             | 3.4            | 4            | 57.4         | 29.35      | 20          | 25                  | 5                           | NA                       | NA          |             |
| 8       | 40.9              | 44.7            | 1.62               | 0.625           | 3              | 3.2          | 19.4         | 17         | 20          | 25                  | 0                           | NA                       | NA          |             |
| 9       | 36.7              | 36.4            | 0.4                | <0.29           | 3.5            | 1.9          | 80.4         | 61         | 45          | 50                  | NA                          | NA                       | NA          |             |
| 10      | 36.5              | 35.7            | 0.95               | 1.11            | 2.7            | 3.3          | 77.3         | 69.7       | 5           | 0                   | 30                          | 16                       | 17          |             |

*Data collected for patient's second time on ustekinumab
Figure 2. Laboratory and BMI response. Hematocrit in patients with (A) augmented dosing and (B) Q8 dosing; CRP in patients with (C) augmented dosing and (D) Q8 dosing; albumin in patients with (E) augmented dosing and (F) Q8 dosing; BMI in patients with (G) augmented dosing and (H) Q8 dosing.
disease exacerbation and increase in maintenance frequency to Q6 resulted in clinical remission. However, more data from subsequent follow ups is needed to determine if disease activity corresponds to dosing frequency and trough level since he had no trough level during previous remission on SCD diet.

Among the three patients on standard dosing for the entire duration of treatment, only one achieved remission. He had ileocolonic as well as symptomatic gastroduodenal CD, which is a relatively rare manifestation and only affects about 2% of CD patients. There are currently no well-established treatment protocols for gastroduodenal CD, and despite treatments with corticosteroid, 6-MP, ASA, and anti-TNF agents, 31% of patients eventually require surgery. We cannot conclude if patient 8’s clinical improvement was secondary to ustekinumab or corticosteroids.

In a previous study by Battat et al. over 75% of adult CD patients needed Q4 week dosing for maintenance of clinical response. This study also demonstrated a positive association of biomarkers and endoscopic improvement with ustekinumab trough levels >4.5 µg/mL. In addition, in a case series of three adult CD patients, Park et al demonstrated an ability to recapture response by dose escalation among patients who lost response to standard ustekinumab dosing regimen. Several observational studies in pediatric IBD patients demonstrate ustekinumab’s efficacy in inducing and maintaining remission. While the majority of patients in both studies had dose frequency escalation, the decision was made based on patient’s lack of clinical response. Even though ustekinumab concentration and antibody level was measured for more than half of the 52 patients studied by Dayan et al., the author noted that there was no timing consistency for these measurements, and there was no correlation between dosing escalation and clinical remission. In contrast, among the 7 patients who required dose escalation in our study, 6 had subtherapeutic drug level on Q6 and Q8 dosing interval, which corresponded with poorly controlled disease activities. All these patients showed clinical response to changing dosing frequency. The two patients who were on standard dosing interval (Q8 weeks), therapeutic drug monitoring (TDM) was not performed and thus we cannot determine if treatment failure was due to subtherapeutic dosing or a primary non-response to ustekinumab. This study demonstrates that TDM can be used to guide dose frequency escalation in patients who show no clinical response or lack of clinical response to ustekinumab. A larger, randomized trial is needed to confirm the role of ustekinumab TDM in pediatric CD patients. Thus, based on our experience and existing literature, we recommend proactively checking trough levels 4 weeks after maintenance therapy initiation to guide dosing frequency early in the treatment course or to consider reactively checking levels and augmenting maintenance dosing interval in patients with sub-optimal or poor response to standard dosing.

Serious adverse effects were rare among our patients despite shorter dosing intervals. Only two patients developed recurrent infections and required hospitalization while on ustekinumab. Even though the patient who was hospitalized for abscesses also had other comorbidities such as maturity onset diabetes of the young, acne, skin picking, psoriasis, and was previously hospitalized twice for recurrent abscesses on certolizumab, ustekinumab could not be ruled out as a cause of these infections. We did not observe any serious infections or cancers in the remaining eight patients, suggesting that ustekinumab is relatively well tolerated even at a higher frequency in pediatric patients.

**Limitations**

Our study is limited by its small size and retrospective nature. Furthermore, induction and maintenance doses were not uniform among all patients. TDM was only performed on six patients, and follow-up trough for five out of those six patients have not been obtained after changes in dosing frequency.

Only six patients had pre- and post-treatment endoscopy, and two of those patients had intestinal surgeries, which might have altered SES-CD scores. Even though abbrPCDAI and other laboratory workups were helpful to correlate disease activities, fecal calprotectin should be added to further assess inflammation.

**Conclusion**

In this retrospective chart review, 7 out of 10 patients with anti-TNF refractory pediatric-onset Crohn’s disease required augmented maintenance doses of ustekinumab to achieve clinical response or remission as measured by abbrPCDAI. The remaining three patients on standard maintenance doses either did not respond or had confounding factors affecting clinical response. Further large, randomized studies with closer therapeutic drug monitoring are needed to assess the relationship between dosing interval, trough levels, and clinical response in the pediatric population. Longer follow up is also needed to assess response once ustekinumab has reached therapeutic level.

**Data availability**

**Underlying data**

Figsshare: Table 1. Baseline characteristics of patients included in the study, https://doi.org/10.6084/m9.figshare.14681013.

Figsshare: Table 2. Ustekinumab dosing, interval, levels, duration of therapy, and complication, https://doi.org/10.6084/m9.figshare.14681028.

Figsshare: Table 3 Clinical response of anti-TNF refractory pediatric Crohn Disease patients on ustekinumab.csv, https://doi.org/10.6084/m9.figshare.14681040.

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Acknowledgements**

The abstract of this work was presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting (October 17-19, 2019, Chicago, IL; abstract 101).
References

1. Ong C, Aw MM, Liwanag MJ, et al.: Rapid rise in the incidence and clinical characteristics of pediatric inflammatory bowel disease in a South-East Asian cohort in Singapore, 1994-2015. J Dig Dis. 2018; 19(7): 395–403. PubMed Abstract | Publisher Full Text

2. Sýkora J, Pomáhacová R, Kreslová M, et al.: Current global trends in the incidence of pediatric-onset inflammatory bowel disease. World J Gastroenterol. 2018; 24(25): 2741–2763. PubMed Abstract | Publisher Full Text | Free Full Text

3. Pozler O, Malý J, Bonova O, et al.: Incidence of Crohn disease in the Czech Republic in the years 1990 to 2001 and assessment of pediatric population with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2006; 42(2): 186-9. PubMed Abstract | Publisher Full Text

4. Pignon B, Sekiš P, Violà S, et al.: Natural history of Crohn’s disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis. 2010; 16(6): 953–61. PubMed Abstract | Publisher Full Text

5. Ruemmele FM, Veres G, Kolho KL, et al.: Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn’s disease. J Crohns Colitis. 2014; 8(10): 1179–1207. PubMed Abstract | Publisher Full Text

6. Cameron F, Wilson M, Basheer N, et al.: Anti-TNF therapy for paediatric IBD: the Scottish national experience. Arch Dis Child. 2015; 100(4): 399–405. PubMed Abstract | Publisher Full Text

7. Grossi V, Lerner T, Griffths A, et al.: Concomitant Use of Immunomodulators Affects the Durability of Infliximab Therapy in Children With Crohn’s Disease. Clin Gastroenterol Hepatol. 2015; 13(10): 1748-1756. PubMed Abstract | Publisher Full Text

8. Feagan BG, Sandborn WJ, Gasink C, et al.: Ustekinumab as Induction and Maintenance Therapy for Crohn’s Disease. N Engl J Med. 2016; 375(20): 1946-1960. PubMed Abstract | Publisher Full Text

9. Bertrand V, El Halte A, Carré D: Efficiency of Ustekinumab in Crohn’s Disease with Severe Psoriasisiform Rash Induced by Biotherapies in an Adolescent. Pediatr Dermatol. 2017; 34(3): e214-e215. PubMed Abstract | Publisher Full Text

10. Riniaw F, Rosenbach Y, Assa A, et al.: Ustekinumab for Resistant Pediatric Crohn Disease. J Pediatr Gastroenterol Nutr. 2016; 62(4): e34-e35. PubMed Abstract | Publisher Full Text

11. Bishop C, Simon H, Suskind D, et al.: Ustekinumab in Pediatric Crohn Disease Patients. J Pediatr Gastroenterol Nutr. 2016; 63(3): 348-51. PubMed Abstract | Publisher Full Text

12. 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(6): 1314–21. PubMed Abstract | Publisher Full Text

13. Shepanski MA, Markowitz JE, Mamula P, et al.: Is an abbreviated Pediatric Crohn’s Disease Activity Index better than the original? J Pediatr Gastroenterol Nutr. 2004; 39(1): 68–72. PubMed Abstract | Publisher Full Text

14. Daperno M, D’Haens G, Van Asche G, et al.: Development and validation of a new, simplified endoscopic activity score for Crohn’s disease: the SES-CD. Gastrointest Endosc. 2004; 60(4): 505-12. PubMed Abstract | Publisher Full Text

15. Roda G, Jharp B, Neeraj N, et al.: Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016; 7(1): e135. PubMed Abstract | Publisher Full Text | Free Full Text

16. Koutroubakis E, Katanos KH: Implementation of the simple endoscopic activity score in Crohn’s disease. Saudi J Gastroenterol. 2016; 22(3): 183-91. PubMed Abstract | Publisher Full Text

17. Geraets M, Coolen JF, Sandborn WJ, et al.: Validation of endoscopic activity scores in patients with Crohn’s disease based on a post hoc analysis of data from SONIC. Gastroenterology. 2013; 145(5): 978-986.e5. PubMed Abstract | Publisher Full Text

18. Battat R, Kogoy IJ, Bessicoff 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(9): 1427-1434.e2. PubMed Abstract | Publisher Full Text

19. Kerur B, Benchimol EI, Fiedler K, et al.: Natural History of Very Early Onset Inflammatory Bowel Disease in North America: A Retrospective Cohort Study. Inflamm Bowel Dis. 2021; 27(3): 295–302. PubMed Abstract | Publisher Full Text | Free Full Text

20. Dayan J, Doolinger M, Benkso 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(1): 61–67. PubMed Abstract | Publisher Full Text | Free Full Text

21. Turner D, Levine A, Walters TD, et al.: Which PDAI Version Best Reflects Intestinal Inflammation in Pediatric Crohn Disease? Pediatr Gastroenterol Nutr. 2017; 64(2): 254-260. PubMed Abstract | Publisher Full Text

22. Nugent FW, Richmond M, Park SK: Crohn’s disease of the duodenum. Gut. 1977; 18(2): 115–120. PubMed Abstract | Publisher Full Text | Free Full Text

23. Murray JJ, Schetz DJ Jr, Nugent PW, et al.: Surgical management of Crohn’s disease involving the duodenum. Am J Surg. 1984; 147(1): 58-65. PubMed Abstract | Publisher Full Text

24. Park S, Evans E, Sandborn WJ, et al.: Ustekinumab IV 6 mg/kg Loading Dose Re-induction Improves Clinical and Endoscopic Response in Crohn’s disease: A Case Series. Am J Gastroenterol. 2018; 113(4): 627-629. PubMed Abstract | Publisher Full Text

25. Cohen A, Najma A, Sant’Anna A, et al.: Ustekinumab for the Treatment of Refractory Pediatric Crohn’s Disease: a Single-Center Experience. Intest Res. 2021; 19(2): 217–224. PubMed Abstract | Publisher Full Text | Free Full Text

26. Do P, Gurrum B, Loo P, et al.: Table 1. Baseline characteristics of patients included in the study. figshare. Dataset. 2020. https://www.doi.org/10.6084/m9.figshare.1468103

27. Do P, Gurrum B, Loo P, et al.: Table 2. Ustekinumab dosing, interval, levels, duration of therapy, and complication. figshare. Dataset. 2020. https://www.doi.org/10.6084/m9.figshare.1468102

28. Do P, Gurrum B, Loo P, et al.: Table 3 Clinical response of anti-TNF refractory pediatric Crohn Disease patients on ustekinumab.csv. figshare. Dataset. 2020. https://www.doi.org/10.6084/m9.figshare.1468104
Open Peer Review

Current Peer Review Status:

Version 2

Reviewer Report 31 August 2021

https://doi.org/10.5256/f1000research.57245.r91519

© 2021 Kellermayer R. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Richard Kellermayer

1 Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
2 Section of Pediatric Gastroenterology, Texas Children's Hospital, Houston, TX, USA
3 USDA/ARS Children's Nutrition Research Center, Houston, TX, USA

The authors have addressed all my concerns appropriately.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, molecular genetics, epigenetics, nutrition, developmental origins of disease, recurrent Clostridioides difficile infection, fecal transplantation, microbiome, microbial therapeutics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 12 April 2021

https://doi.org/10.5256/f1000research.25033.r62949

© 2021 Elkadri A. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abdul Elkadri

Medical College of Wisconsin, Milwaukee, WI, USA
This study reviews retrospectively the experience of one pediatric institution with ustekinumab in Crohn’s disease patients. This is an understudied population with paucity of data. Interestingly, it showed good response in 7/10 patients, but also showed that there was a need for shortened intervals of dosing. This shortened interval of dosing was shown previously in one of the adult studies cited and suggests that there needs to be more studies to support this shortened interval. The review is limited by the lack of comprehensive endoscopic data for all patients, and by the lack of comprehensive data for therapeutic drug monitoring to try to prove the hypothesis that shortened intervals lead to remission and clinical response (with resulting increased drug levels). The retrospective nature of this paper makes the data limited in its ability to prove the hypothesis, but the data is still reviewed well and with details all available to show what the authors have stated. The population is somewhat heterogeneous in nature, limiting the ability to identify a subpopulation where the response is higher.

Due to the small number of patients, the manuscript is by default limited to a descriptive review which the authors have done properly in this manuscript. The data needs to be published to expand the available literature on this medication in this population.

The current version of the manuscript is appropriate for indexing.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric inflammatory bowel Disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 18 May 2020

https://doi.org/10.5256/f1000research.25033.r62953
Phinga Do and colleagues, with the leadership of Bhaskar Gurram, give a nice summary on 10 pediatric Crohn's disease patients, refractory to anti-TNF biologic therapy, who were treated with ustekinumab. Such real life observations on the off label use of new biologic agents in pediatric inflammatory bowel disease (IBD) patients are rather important. Their conclusions coincide with our subjective observation that pediatric IBD patients require a more intensified use of ustekinumab than the manufacturer's guidance, in order to achieve drug levels that have been found to associate with improved outcomes in adult patients. There are a couple of recommendations, which may further improve the manuscript.

1. In the Methods section, please clarify which laboratory and what methodology was used (especially for ustekinumab therapeutic drug monitoring) for the laboratory measurements discussed in the paper.

2. Very early onset (VEO) IBD is more and more considered a disease category of its own within IBD. Consider excluding the VEO-IBD (patient 1) case from this cohort, or highlight the case as a variant.

3. Excluding the brief 4 week course of patient 6 from the table and discussion is recommended. The treatment course was too short to make any conclusions. The comment below the figure is important to keep, however, to clarify that patient 6 was exposed to ustekinumab 2 years prior to the treatment course examined.

4. In Table 1, or in a separate table, it would be useful to clarify the type of anti-TNF failure for each patient and each anti-TNF biologic, respectively. Primary non-response could be due to rapid antibody development or primary biological non-response. The same is true for secondary non-response (i.e. late development of antibodies, or immune pathway shift). It is fine to state unknown/clinical if level and antibody for the anti-TNF agent was not examined.

5. In the results, consider omitting the complicated description of dosing, since Table 2 describes that in detail.

6. Both figures are complicated, and the results those depict could be easily described and followed in writing within the Results section. Omitting the figures is recommended.

7. The clinical outcomes are difficult to follow based on the separation of the patients by augmented ustekinumab treatment versus not. Separating the patients by responders vs. non-responders, and examining ustekinumab dosing differences between the 2 groups is recommended. If I am not mistaken, and even if the patient 1 (VEO-IBD) case is excluded, there were 7 responders (6 on intensified ustekinumab therapy) and 2 non-responders (all
on conventional ustekinumab treatment). These results, if compared by Chi squared testing, significantly favor (p=0.0233) treatment intensification in order to achieve clinical response.

8. There are parts of the discussion, which continue specific patient outcome descriptions. This should be moved to the Results section. The discussion should only draw general conclusions from what has been presented in the results and compare the findings to the existing literature.

9. Include in the discussion, more recent similar studies, such as the ones below, and highlight the novelties of the case series presented within this work compared to other pediatric cohorts:

1. Real World Experience With Ustekinumab in Children and Young Adults at a Tertiary Care Pediatric Inflammatory Bowel Disease Center. Dayan JR et al. J Pediatr Gastroenterol Nutr. (2019)¹
2. Ustekinumab for the treatment of refractory pediatric Crohn's disease: a single-center experience. Cohen A, Ahmed N, Sant'Anna A.. Intest Res. 2020 Apr 22.²

References
1. Dayan J, Dolinger M, Benkov K, Dunkin D, et al.: Real World Experience With Ustekinumab in Children and Young Adults at a Tertiary Care Pediatric Inflammatory Bowel Disease Center. Journal of Pediatric Gastroenterology and Nutrition. 2019; 69 (1): 61-67 Publisher Full Text
2. Cohen A, Ahmed N, Sant'Anna A: Ustekinumab for the treatment of refractory pediatric Crohn's disease: a single-center experience. Intestinal Research. 2020. Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?  
Partly

Is the study design appropriate and is the work technically sound?  
Yes

Are sufficient details of methods and analysis provided to allow replication by others?  
Partly

If applicable, is the statistical analysis and its interpretation appropriate?  
Partly

Are all the source data underlying the results available to ensure full reproducibility?  
Partly

Are the conclusions drawn adequately supported by the results?  
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, molecular
genetics, epigenetics, nutrition, developmental origins of disease, recurrent Clostridioides difficile infection, fecal transplantation, microbiome, microbial therapeutics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 May 2021

phinga do, Children's Health Medical Center Dallas, Dallas, USA

1. In the Methods section, please clarify which laboratory and what methodology was used (especially for ustekinumab therapeutic drug monitoring) for the laboratory measurements discussed in the paper.

   All of the tests were done either by Miraca or Inform Diagnostics. Both these labs use Automated ELISA assay for simultaneous antibody and drug levels.

2. Very early onset (VEO) IBD is more and more considered a disease category of its own within IBD. Consider excluding the VEO-IBD (patient 1) case from this cohort, or highlight the case as a variant.

   Although some patients with VEOIBD might behave differently than conventional-onset IBD patients (onset>10 years of age), there is still significant overlap with their disease behavior and response to therapy. Moreover, although the patient 1 included in the current study had onset at 2 years of age, he was started on ustekinumab at 9 years age. Inflamm Bowel Dis 2021 Feb 16;27(3):295-302. doi: 10.1093/ibd/izaa080.

3. Excluding the brief 4-week course of patient 6 from the table and discussion is recommended. The treatment course was too short to make any conclusions. The comment below the figure is important to keep, however, to clarify that patient 6 was exposed to ustekinumab 2 years prior to the treatment course examined.

   We will remove this part. Agree that it does not add much aside from noting that there's prior exposure.

4. In Table 1, or in a separate table, it would be useful to clarify the type of anti-TNF failure for each patient and each anti-TNF biologic, respectively. Primary non-response could be due to rapid antibody development or primary biological non-response. The same is true for secondary non-response (i.e. late development of antibodies, or immune pathway shift). It is fine to state unknown/clinical if level and antibody for the anti-TNF agent was not examined.

   Table 1 has been modified to include more specific reasons for anti-TNF failure.

5. In the results, consider omitting the complicated description of dosing, since Table 2 describes that in detail.
The results section has been edited to omit dosing descriptions.

6. Both figures are complicated, and the results those depict could be easily described and followed in writing within the Results section. Omitting the figures is recommended.

We believe that the figures compliment the text and some readers prefer just to look at the tables and pictures. They provide visual aid and show a clear trend of improvement for patients on augmented dosing.

7. The clinical outcomes are difficult to follow based on the separation of the patients by augmented ustekinumab treatment versus not. Separating the patients by responders vs. non-responders and examining ustekinumab dosing differences between the 2 groups is recommended. If I am not mistaken, and even if the patient 1 (VEO-IBD) case is excluded, there were 7 responders (6 on intensified ustekinumab therapy) and 2 non-responders (all on conventional ustekinumab treatment). These results, if compared by Chi squared testing, significantly favor \( p=0.0233 \) treatment intensification in order to achieve clinical response.

We did organize it by responder vs non responder initially but found that organizing by augmented vs standard dosing shows a clearer trend. Moreover, what we want to point out to the readers through this paper is that most pediatric patients in our cohort needed higher dose than the standard dosing. In addition, we cannot say if patient 8 (the one with duodenal stricture) is an ustekinumab responder or not and will require 3 distinct categories (responder, non-responder, and indeterminant). All 7 responders were on augmented dose.

8. There are parts of the discussion, which continue specific patient outcome descriptions. This should be moved to the Results section. The discussion should only draw general conclusions from what has been presented in the results and compare the findings to the existing literature.

The text has been reorganized.

9. Include in the discussion, more recent similar studies, such as the ones below, and highlight the novelties of the case series presented within this work compared to other pediatric cohorts:

Edited to include these 2 studies.

**Competing Interests:** None
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com