Journal of Crohn's and Colitis, 2019, 578–584
doi:10.1093/ecco-jcc/jjy206
Advance Access publication December 12, 2018
Original Article

Original Article

Management of Paediatric Patients With Medically Refractory Crohn's Disease Using Ustekinumab: A Multi-Centred Cohort Study

Mallory Chavannes,[a,b] Christine Martinez-Vinson,[c] Lara Hart,[d] Nicole Kaniki,[e] Che-Yung Chao,[d,f] Sally Lawrence,[g] Kevan Jacobson,[g] Jean-Pierre Hugot,[c] Jérome Viala,[c,h] Colette Deslandres,[a,i] Prevost Jantchou,[a,i] Ernest G. Seidman[d]

[a]Department of Paediatrics, Sainte-Justine UHC, University of Montreal, QC, Canada [b]Department of Paediatrics, Children Hospital of Los Angeles, Los Angeles, CA, USA [c]Division of Paediatric Gastroenterology, Hôpital Robert-Debré, Assistance Publique-Hôpitaux de Paris, Paris, France [d]Montreal Children's Hospital, Department of Paediatrics, McGill University, Montreal, QC, Canada [e]Research Western, Western University, London, ON, Canada [f]Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, QLD, Australia [g]Division of Paediatric Gastroenterology Hepatology and Nutrition, BC Children's Hospital, University of British Columbia, Vancouver, BC, Canada [h]UFR de Médecine, Université Paris Diderot-Sorbonne Paris Cité, Paris, France [i]Research Centre of CHU Sainte-Justine, University of Montreal, Montreal, QCc, Canada

Corresponding author: Mallory Chavannes, MD, MHSc, FRCPC, Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Los Angeles, University of Southern California, 46504650 Sunset Boulevard, Mailstop #78, Los Angeles [California], CA, USA 90027. Email: mchavannes@chla.usc.edu

Conference proceedings: World Congress of Paediatric Gastroenterology, Hepatology and Nutrition [WCPGHAN] 2016, Montreal, QC, Canada, poster, ESPGHAN.

Abstract

Background: Ustekinumab [UST] is effective in the treatment of adults with moderate to severe Crohn's disease [CD]. There is a paucity of data on its use in children.
Aim: To evaluate the response to UST in children with moderate to severe CD.
Methods: This multicentre retrospective cohort study identified children under 18 years old with CD, who received open-labelled subcutaneous UST. The primary outcome was changes in mean abbreviated Paediatric Crohn's Disease Activity Index [aPCDAI] between baseline and 3 and 12 months, and rate of clinical remission at 3 and 12 months. Secondary outcomes were clinical response at the same time points, changes in C-reactive protein [CRP] and albumin, improvement in growth parameters, and rate of adverse events.
Results: A total of 44 patients who failed at least one biological treatment were identified. Linear mixed model [LMM] analysis revealed a statistically significant effect of UST ($X2[1] = 42.7$, $p = 1.2 \times 10^{-8}$) which lowered the aPCDAI scores by about 16 ± 2.7 at 3 months, and 19.6 ± 2.9 at 12 months. At 12 months, 38.6% of the patients achieved clinical remission and 47.8% achieved clinical response. There was a significant increase in mean weight z-score of 0.48 [±0.13] [p <0.001] and in mean body mass index [BMI] z score of 0.66 [±0.16] [p <0.001]. The probability of remaining on UST at 12 months was 76.9%. The rate of adverse events was 12.4 per 1000 patient-months.

Conclusions: Subcutaneous UST should be considered a viable therapeutic option for paediatric patients who are refractory to other biological agents. Prospective randomised trials are needed.

Key Words: Ustekinumab; Crohn's disease; paediatric

1. Introduction

Crohn's disease [CD] is an incurable chronic inflammatory bowel disease with 25% of patients being diagnosed under the age of 20 years.[1] The achievement of deep remission through the use of medical therapies increases the chance of avoiding irreversible gastrointestinal damage, complications, and surgeries.[2,3] Despite an expanding number of therapies available, anti-tumour necrosis factor [TNF] agents remain the only biological treatment validated for use in paediatric patients with moderate to severe CD.[4,5] Despite their established effectiveness, there is a primary non-response rate of 10–30% and a secondary loss of response rate of 13–40%.[6–10] One new therapeutic option is ustekinumab [UST, Stelara®, Janssen, Titusville, NJ, USA]. UST is a human IgG1k monoclonal antibody that blocks the activity of interleukin 12/23 through their shared p40 subunit.[11,12] Clinical trials assessing the efficacy of UST in adults with CD have demonstrated up to a 35% clinical response at Week 6 in patients previously exposed to biological agents.[13,14] Among those who responded, up to 53% maintained clinical remission at Week 44.[12] However, the use of this medication in paediatric CD has not been well studied. Moreover, access to UST in children continues to be limited to a compassionate basis.

The majority of the literature on the use of UST in paediatrics is in rheumatological or dermatological conditions. A phase 3 clinical trial in adolescents with plaque psoriasis reported a high clinical response of up to 80.66%.[15] There was no difference in the rate of adverse events [AE] between the treatment and placebo groups, the most common being infections.[15] No randomised clinical trials have yet been reported in paediatric CD, although a large randomised trial and a prospective study are both ongoing [clinicaltrial.gov ID: NCT02968108].[16] A few case reports and small case series have been published, which observed a clinical response and improvement in growth and biomarkers in 50% of patients on UST.[17–19] Preliminary data from one small prospective paediatric study were also promising, showing clinical response of 71.4% and clinical remission in 42.9% at 16 weeks.[16]

Despite the lack of robust data, UST is being used off-label in paediatric patients with CD who are refractory or intolerant to conventional biological agents. Our objectives were therefore to: 1] assess the effectiveness and safety of UST in paediatric patients with medically refractory CD; and 2] try to identify risk factors predicting discontinuation of UST.

2. Methods

This retrospective cohort study included all patients less than 18 years of age who initiated open-labelled UST in four paediatric tertiary care centres. We included consecutive patients who initiated UST between January 2014 and December 2016 and were thereafter followed for at least 12 months or until the medication was discontinued [which may have been less than 12 months, when they were considered treatment failures]. Data were collected until February 2018. Ethics approval for the study was obtained from the ethics committee of each centre. Inclusion criteria were UST-treated patients who previously failed to respond, lost response, or were intolerant to at least one biological treatment. De-identified clinical data pertaining to disease phenotype, previous medication history, and baseline biochemical markers were extracted from the patients' paper-based or electronic records. The presence of growth failure before starting UST was recorded. Growth failure was defined as a deceleration in weight or height velocity, crossing of at least one major percentile for height or weight on the WHO growth chart. Clinical information and laboratory data were collected at UST initiation [baseline] and during follow-up at 3- and 12-month visits. Laboratory data included serum C-reactive protein [CRP] and albumin. Considering the different assays used to evaluate CRP, we considered this serum marker as elevated when the value was more than 5 mg/L

2.1. Primary outcome

Disease activity was evaluated using the abbreviated Paediatric Crohn's Disease Activity Index [aPCDAI], a validated clinical score that excludes the blood work component of the original PCDAI. It was chosen because the erythrocyte sedimentation rate [ESR] is not routinely performed in all participating centres. As previously described,[20] a score of <10 is indicative of clinical remission, 10 to 15 indicates mild disease, 15 to 25 moderate disease, and over 25 severe disease activity. A moderate improvement was defined as a change in score ≥15.[20] The primary outcome was defined as the percentage of patients achieving clinical remission over the first 12 months of therapy. Improvement in scores from baseline to 3 were also assessed for significance.

2.2. Secondary outcomes

Secondary outcomes included: 1] the rate of clinical response, defined as a decrease in aPCDAI ≥15; 2] proportion of patients whose CRP normalised; 3] the changes in albumin levels between baseline and follow-up visits at 3 and 12 months; and 4] the rate of steroid-free remission at 12 months, defined as patients off systemic steroids and with an aPCDAI <10. In addition, we assessed changes in height, weight, and body mass index [BMI], using Z-scores based on WHO standards between baseline and 12 months. All adverse events were recorded over the course of the follow-up period.

2.3. Statistical analysis

All statistical analyses were performed using RStudio software [version 1.0.136® RStudio Inc,; https://www.rstudio.com/]. A summary of categorical data was performed using frequency calculation, and percentages and distribution of quantitative data were described using medians and interquartile range as appropriate. Changes in continuous data for improvement of scores from baseline to 3 and 12 months assessment points were completed using a linear mixed model [LMM] analysis which accounted for missing data and compared change over time using a repeated measures analysis of variance [ANOVA]. The LMM, used to determine the relationship between aPCDAI scores and each time point, included sex and age as fixed effects; with random effects being the subjects, albumin levels at baseline [normal vs low], frequency of UST administration [q4 vs q8 weeks], history of intestinal resection before UST, disease severity

at baseline, complicated phenotype, presence of ileocolonic disease at baseline, concomitant immunomodulator use, and early response to treatment at 3 months. Visual inspection of residual plots was used to assess deviations from homoscedasticity and normality; *p*-values were obtained by computing likelihood ratio tests of the experimental model [i.e. including the fixed effects as well as the random effects] against a null model [i.e. a model in which the continuous variable was predicted only by the random effects]. Differences between categorical data at different time points were analysed using the McNemar chi square test. Durability of UST treatment was analysed using KaplanMeier curves. A *p*-value of less than 0.05 was considered statistically significant. A logistic regression model was created to assess predictive variables associated with treatment failure, using drug discontinuation as a surrogate. The following variables were chosen a priori: age at diagnosis, disease duration, low CRP at baseline, disease phenotype, disease location, concurrent immunomodulator treatment, cumulative induction dose per body weight [mg/kg], frequency of UST administration [q4 weeks vs q8 weeks]. The C-statistic was use to assess the fit of the model, with a value closest to 1 indicating that the model had a good fit and strong predictive capacity. Finally, the cumulative rate of adverse events associated with UST exposure was calculated on an intent-to-treat basis.

2.4. Missing data

We performed an intention-to-treat analysis. For calculation of the primary outcome measures, missing data scores were accounted for using the LMM analysis for continuous data. Considering that the likelihood of a poor outcome was higher in patients with missing data, we considered that conventional methods [e.g. latest observation carried forward, mean imputation, etc.] were not sufficiently conservative to determine treatment effect. Patients with missing disease activity data were therefore imputed as having active disease [worst outcome]. Missing secondary outcomes for continuous variables were also accounted for using LMM. Albumin was assessed as a latest observation carried forward and latest observation carried backward, promoting a conservative analysis of no change in status. CRP was assessed as dichotomous variable [normal vs elevated] and was also imputed as latest observation carried forward, as patients with active disease and a normal CRP at study onset were likely not able to produce an elevated CRP.[21] Finally, steroid exposure was considered positive when the information was missing, or UST was stopped. Therefore, steroid exposure was evaluated only in patients who remained on UST for at least 12 months.

3. Results

3.1. Patient characteristics and UST regimens

From the four hospitals, we identified 44 patients who received UST for the treatment of medically refractory CD. Their demographic information is summarised in Table 1. All patients failed at least one anti-TNF agent; 12 patients [27.3%] stopped therapy within the first year of treatment; the remainder were followed for at least 12 months. The median observed treatment duration on UST was 13 months (interquartile range [IQR] 10.3–21.3). Both the induction and maintenance doses were administered subcutaneously in all patients. In addition, 21 [47.7%] patients were on corticosteroids at the initiation of UST. Overall, six different induction regimens were used [Table 2]. The most common induction dosing used was 90 mg weekly for 3 weeks followed by a maintenance dose of 90 mg q8 weeks. All induction protocols were completed within 4 weeks.

Table 1. Demographics and clinical characteristics of paediatric Crohn's disease patients at initiation of ustekinumab [UST]

Patient characteristics	*n* = 44
Male, *n* [%]	22 [50]
Median age [IQR] at diagnosis [y]	11 [8–13]
Median age [IQR] at initiation of UST [y]	16 [13–17]
Median [IQR] observed duration UST [mo]	13 [10.3–21.3]
Disease location [Paris Classification]	*n* [%]
L1	3 [6.8]
L2	20 [45.5]
L3	21 [47.7]
L4a	14 [31.8]
L4b	5 [11.4]
Perianal	16 [36.4]
Disease phenotype [Paris Classification]	*n* [%]
B1	32 [72.7]
B2	9 [20.5]
B3	3 [6.8]
Growth failure, *n* [%]	18 [40.9]
Extraintestinal manifestations, *n* [%]	11 [25]
Previous surgery, *n* [%]	9 [20.4]
Previous immunomodulators, *n* [%]	
Azathioprine	33 [75]
Methotrexate	22 [54.5]
Previous anti-TNF exposure, *n* [%]	
Infliximab	41 [93.1]
Adalimumab	29 [65.9]
Certolizumab	1 [2.3]
Golimumab	1 [2.3]
Previous anti-integrin exposure, *n* [%]	
Vedolizumab	3 [6.8]
Other therapies, *n* [%]	
Thalidomide	2 [4.5]
Tacrolimus	5 [11.4]
Concomitant immunosuppression, *n* [%]	
Azathioprine	3 [6.8]
Methotrexate	10 [22.7]
Steroid exposure at initiation, *n* [%]	20 [45.5]
aPCDAI [median, IQR]	27.5 [20–40]
Albumin, g/L [median, IQR]	34.5 [32–38.9]
CRP, mg/L [median, IQR]	17 [9.5–25.5]

IQR, interquartile range; y, years; mo, months; TNF, tumour necrosis factor; aPCDAI, abbreviated Paediatric Crohn's Disease Activity Index; CRP, C-reactive protein.

By the time of the latest follow-up, 13/44 [29.5%] patients were dose-escalated to a maintenance frequency of every 4 weeks, because of persistent symptoms.

3.2. Primary outcome

Four patients [9.1%] had an aPCDAI indicating clinical remission at baseline. However, one patient had active disease on colonoscopy, two had an elevated faecal calprotectin, and one had persistent growth failure despite therapy, which warranted the initiation of UST. Clinical remission was achieved in 16/44 patients [36.4%, $p = 0.006$] at 3 months and 17/44 patients [38.6%, $p = 0.006$] were in clinical remission at 12 months [Figure 1]. When applying the LMM, visual inspection of residual plots did not reveal any obvious deviation from homoscedasticity or normality. The analysis revealed a statistically and clinically significant effect of UST ($X2[1] = 42.7$, $p = 1.2 \times 10^{-8}$) with improvement of aPCDAI scores [± standard error] by 16.0 ± 2.7 points at 3 months, and 19.6 ± 2.9 points at 12 months.

Table 2. Subcutaneous ustekinumab induction regimens used for paediatric Crohn's disease by the different included medical centres.

	90 mg at Weeks 0,1,2	90 mg at Weeks 0,2,4	90 mg at Weeks 0,4	45 mg at Weeks 0,1,2	270 mg at Week 0 and 180 mg at Weeks 1,2	270 mg at Week 0 and180 mg at Weeks 3,4	Total [%]
Centre A	1	1		5	2	1	10 [23.8]
Centre B	8				1		9 [21.4]
Centre C	7				2		9 [21.4]
Centre D		8	6				14 [33.3]
Total [%]	16 [38.1]	9 [21.4]	6 [14.3]	5 [11.9]	5 [11.9]	1 [2.4]	

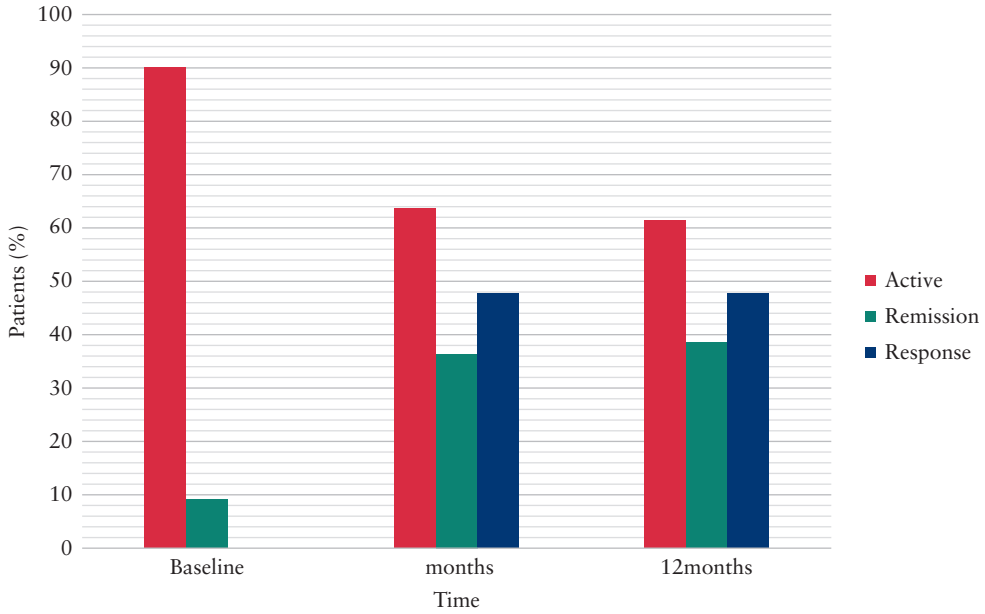

Figure 1. Short- and long-term remission and response rates [%] based on abbreviated Paediatric Crohn's Disease Activity Index [aPCDAI]. Red bar: patients with active disease defined as aPCDAI ≥10; green bar: patients in remission defined as aPCDAI <10; blue bar: patients demonstrating clinical response, defined as drop in aPCDAI ≥15.

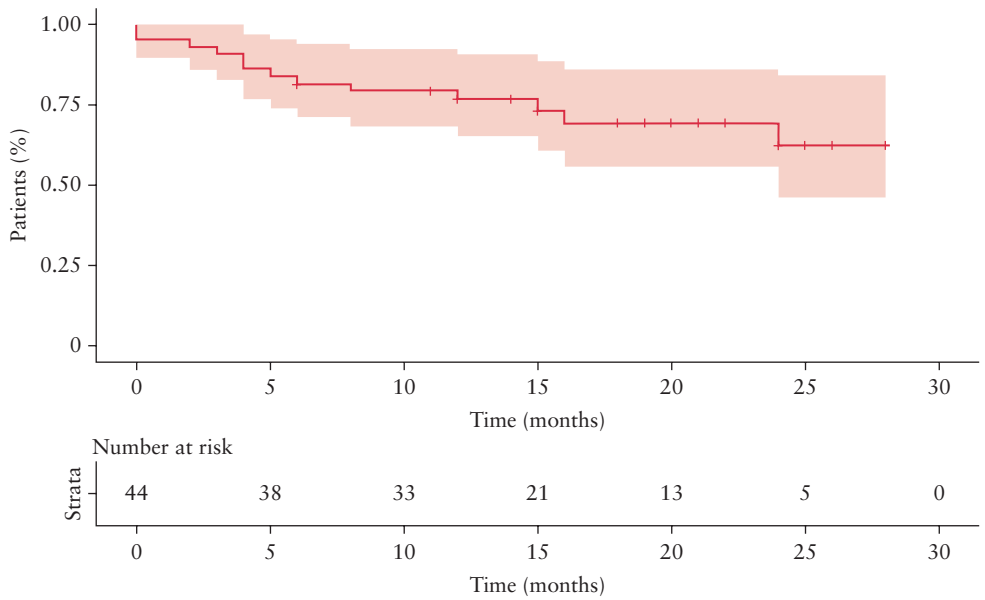

Figure 2. Durability of response to ustekinumab over the total follow-up time of the paediatric Crohn disease cohort. Red line: % patients over time; pink box: confidence interval.

3.3. Secondary outcomes

A clinical response was seen in 21/44 [47.8%] patients at both 3 and 12 months of treatment [Figure 1]. The probability of remaining on UST by 12 months was 76.9% (95% confidence interval [CI]: 65.3–90.6%) [Figure 2].

At study onset, 14 [31.8%] patients had a normal CRP. Among the 30 with an elevated baseline CRP, the test normalised in 10 at 3 months [33.3%, p = 0.004] and in 8/30 [26.7%, p = 0.01] at 12 months. Ten patients [22.7%] were in clinical remission and had a normal CRP at 12 months. The median [IQR] albumin level was 34.5 g/L [32.0–38.9] at baseline, 36.7 g/L [34.2–41.1] at 3 months, and 40.2 g/L [38.0–43.0] at 12 months. LMM analysis of the change in albumin levels demonstrated significant increases of 2.7 g/L [±0.94, p = 0.0147] at 3 months, and 5.3 g/L [±0.99, p <0.0001] at 12 months.

Ten patients discontinued UST before 12 months. Looking at those who remained on treatment, 13/32 [40.6%] were on a steroid at onset of treatment and 5/32 [15.6%] were on a steroid by the end of the year [p = 0.06]; 12/44 [27.3%] were in steroid-free remission at 12 months.

3.4. Growth

The growth parameters are summarised in Table 3. When imputing for missing data, the LMM showed an increase of 0.072 [±0.044] height Z-scores from baseline to 12 months [p = 0.2441]. There was a significant increase of 0.48 [±0.13] in weight Z-scores from baseline to 12 months [p = 0.0008] and a significant increase in BMI Z-score of 0.66 [±0.16] from baseline to 12 months [p = 0.0003].

Before UST treatment, 18/44 patients [40.9%] were identified as having growth failure. After imputation by LMM, we found a significant increase in weight Z-scores of 0.81 ± 0.19 [p = 0.0001] from baseline to 12 months for patients who initially were qualified as having growth failure. However, although the mean weight Z-score of patients without growth failure increased by 0.25 ± 16, that change was not significant [p = 0.62]. Both groups did not significantly increase in height Z-score over the first 12 months of treatment, with the group with growth failure gaining 0.16 ± 0.07 [p = 0.17], and those without growth failure gaining 0.003 ± 0.057 [p = 1.0]. The mean BMI Z-score significantly increased by 1.11 ± 0.25 [p = 0.0004] for patients with growth failure at onset, but the increase in patients who had no growth failure was not significant [0.34 ± 0.20, p = 0.55].

The mean Z-score values for each of the growth parameters were compared at baseline and at 12 months between the growth failure and no growth failure groups. Comparing the two groups with each other, there was a significant difference in mean height Z-scores of 1.62 ± 0.36 [p = 0.0007] at baseline and of 1.46 ± 0.36, p = 0.0027 at 12 months between the two. Although their weight was significantly different at baseline [1.73 ± 0.39, p = 0.0006], the mean weight Z-scores of the two groups were not statistically different at 12 months [1.18 ± 0.40, p = 0.053]. Similarly, the difference in mean BMI Z-scores, which were statistically different at baseline [1.18 ± 0.38, p = 0.0294], decreased at 12 months [0.42 ± 0.40, p = 0.9035]. This may imply some catch-up weight gain in the group with growth failure.

Table 3. Summary of growth parameters, expressed as Z-scores, at baseline and at 12 months.

	Baseline	12 months
Height, whole cohort [IQR]	-0.68 [-1.95–0.23]	-0.82 [-1.95–0.27]
Weight, whole cohort [IQR]	-0.61 [-2.16–0.31]	-0.05 [-1.48–0.69]
BMI, whole cohort [IQR]	-0.66 [-1.61–0.38]	0.18 [-0.63–1.04]
Height, growth failure [IQR]	-1.74 [-2.47–-0.87]	-1.73 [-2.21–-0.95]
Weight, growth failure [IQR]	-1.76 [-2.61–-1.25]	-0.84 [-1.75–-0.21]
BMI, growth failure [IQR]	-1.56 [-2.05–-0.43]	0.10 [-0.59–1.26]
Height, no growth failure [IQR]	-0.10 [-0.68–0.64]	-0.09 [-1.28–0.45]
Weight, no growth failure [IQR]	0.07 [-0.61–0.59]	0.29 [-0.97–1.04]
BMI, no growth failure [IQR]	-0.10 [-0.85–0.67]	0.21 [-0.38–0.96]

IQR, interquartile range; BMI, body mass index.

3.5. Adverse events

A serious adverse event was reported in two patients who received only one induction dose of UST, though the association with the medication was not clear. One patient developed a perianal abscess and the other had worsening of both chronic recurrent multifocal osteomyelitis and cutaneous psoriasis. There were mild adverse events in six others who continued UST treatment after the induction period. Two patients reported migraines, after 1 and 3 months on treatment. Two others reported flares of scalp psoriasis. A fifth patient reported non-persistent bilateral feet paraesthesia after 3 months on treatment. The sixth patient reported symptoms consistent with chronic rhinitis. The rate of adverse events was 12.4 per 1000 patient-months of follow-up. During the study period, 13/44 [29.5%] of patients ceased UST during the maintenance phase, in a median time of 13 months [IQR 10.3–21.3 months]. Adverse events were not the cause of medication cessation during the maintenance phase. Rather, they all discontinued UST due to poor clinical response. Four [9.1%] patients required surgery during the follow-up period, two of whom continued on UST therapy in the postoperative period.

3.6. Factors associated with the risk of UST failure

A multivariate logistic regression was calculated to evaluate the predictors of failure of UST, using discontinuation as a surrogate. The C-statistic of the model as described above was 0.90. A higher induction dose per body weight [mg/kg] was protective against drug discontinuation (odds ratio [OR] = 0.53, 95% CI 0.27–0.84). However, disease duration, use of combination therapy with an immunomodulator, a complicated disease phenotype [either stricturing or fistulising disease], ileocolonic disease, age at diagnosis, high CRP at baseline, and disease activity were not significant predictors of medication discontinuation. The result of the logistic regression is summarised in Table 4.

Table 4. Odds ratios [OR] associated with element of multivariate logistic regression to determine factors predictive of treatment failure with ustekinumab [UST].

	OR	95% confidence interval	p-Value
Total induction dose [mg/kg]	0.53	0.28–0.84	0.0211
Disease duration [years]	1.25	0.76–2.19	0.3960
Concurrent immunomodulator	0.87	0.05–13.24	0.9223
Complicated phenotype	0.04	0.0004–0.75	0.0764
Ileocolonic disease	0.36	0.034–2.87	0.3512
Older age at diagnosis	0.87	0.54–1.34	0.5318
Elevated C-reactive protein at baseline	0.53	0.06–4.34	0.5496
Increased disease activity	0.97	0.89–1.06	0.5285
UST given q4weeks	0.23	0.02–1.52	0.1516

4. Discussion

This paediatric study on the use of UST provides evidence for favourable response and remission rates in cases of CD refractory to conventional biological agents. Nearly 40% of the cohort reached clinical remission at 12 months, with a significant drop in aPCDAI of nearly 20 points at 12 months. Furthermore, for the subgroup of children identified as having growth failure at the onset of UST, weight and BMI Z-scores significantly improved at 12 months.

To date, this report is the largest study on the use of UST in paediatric CD. A systematic search revealed only six reported cases, with similar findings to our study.[16–19] Among these, three of six reached clinical remission with improvement in biochemical profiles, whereas the other three did not improve. Two of the three patients who attained clinical remission also had a significant improvement in growth. This is similar to our findings of significant improvement in weight and BMI for the whole cohort and for children initially presenting with growth failure at the beginning of therapy, who caught up with their peers after a year on treatment. Similarly, preliminary results of a prospective study of UST use in 25 children, using intravenous induction, demonstrated a clinical response of 52% at Week 6 and 45% at latest follow-up.[16]

The results of our study show a slightly lower response rate than the real-world experience of the use of subcutaneous UST in the management of refractory CD in adults.[22,23] Wils *et al.*[22] assessed the effectiveness of UST in a large multicentre retrospective cohort study in adults. They found that 65% experienced a clinical benefit at 3 months. The probability of maintaining the clinical benefit was 93% at 6 and 68% at 12 months. In a study from a single tertiary centre, Kopylov *et al.*[24] reported a response rate of 73.6% after induction, with 64.5% still responding at 6 months. Patients had a loss of response rate of 35%, with a median time to loss of response of 47.4 weeks.

In the cohort of UST responders, we found that CRP and albumin significantly improved at both 3 and 12 months' follow-up. This was also observed for CRP in the UNITI 1/2 and IM-UNITI trials.[13] A retrospective study in adults showed a decrease in CRP in 95% of patients with CD responding to subcutaneous UST, and CRP normalised in 41% of them.[22] Similarly, Kopylov *et al.* found that CRP decreased in all clinical responders who had elevated pre-treatment levels of this biomarker.[24] As most of the patients in this latter cohort had colonic involvement and a protein-losing enteropathy, it was reassuring to note that their albumin levels normalised on UST. This is particularly relevant since we did not have enough stool samples to reliably analyse change in faecal calprotectin, a surrogate marker of luminal disease activity.[25]

As in retrospective adult CD trials with UST, there were a number of different induction regimens used for this cohort. In adult patients, the induction schedule and dosing did not impact on UST response rates.[22,24,26,27] In the study by Wils *et al.*, 13 different induction regimens were used, the most common being 90 mg of UST given at Week 0 and Week 4 in nearly half of the cohort. They did not find a significant association between induction regimen and clinical outcome at 3 months.[22] However, using a multiple logistic regression, the total induction dose for our paediatric patients was significantly associated with the rate of medication discontinuation. A higher dose at induction was associated with a lower discontinuation rate. In clinical practice, one might mistakenly consider UST ineffective when in fact the patient is under-dosed. This highlights the importance of optimising the induction dose for the patient's weight, and why a weight-based intravenous induction regimen may be more effective than the subcutaneous regimen. Further studies are important to determine the optimal dose in paediatric patients.

In this study, 30% of the patients discontinued the medication, used as a surrogate for failure. Aside from Harris *et al.*, who reported a low rate [6%] of medication discontinuation, our paediatric cohort was comparable to other adult CD studies.[25–28] Using multiple logistic regression analysis, the total induction dose adjusted for weight [mg/kg] was the only significant variable protective against the discontinuation of UST [OR 0.5 95% CI = 0.06–4.3]. Disease phenotype, location, and activity, as well as use of combination therapy were not predictive of treatment failure. These results slightly contrast with adult reports, where induction dose and regimen were not significant predictors of response or medication discontinuation. Neither were disease location, baseline CRP, concomitant use of corticosteroids, and patient weight. However, these studies did show that disease severity at induction (HarveyBradshaw Index [HBI] >7) and stricturing phenotype predicted loss of response.[26,27]

The favourable safety profile of UST in our paediatric cohort is in agreement with the adult data on UST for psoriasis and CD.[26,28,29] Headache was the most common side effect in this study, as was reported in the CERTIFI adult study.[12] Viral infections of the upper respiratory tract, often cited as a common side effect, were not seen in our paediatric patients.[22,27,29] Neuropathic pain, similar to the paraesthesia seen in one of our patients, was also reported in one adult.[26] Some patients from the current cohort had flares of psoriasis. Similarly, psoriasis has been reported as a side effect in adult patients, usually without having to discontinue therapy.[30–32] In one paediatric prospective study, three patients experienced side effects, two having fistula or abscess and the third experiencing severe fatigue. Only one of these three patients had to discontinue UST.[16]

There are several limitations concerning this study. One is the retrospective design. However, our data are similar to the results of adult retrospective studies and randomised clinical trials.[14,24] Endoscopies to demonstrate mucosal healing or routine faecal calprotectin as a surrogate marker are lacking. However, clinical response indices and biochemical markers [CRP, albumin], as well as assessment of weight and BMI Z-scores reported, are important indicators of satisfactory response in our paediatric patients. This is especially relevant in patients who had previously had growth failure. Although this is the largest reported paediatric CD cohort treated with UST, the sample size is comparatively limited. Large prospective, randomised controlled studies using different dosing regimens are necessary to better define the optimal effect of UST on clinical response, mucosal healing, and growth in paediatric patients. The different induction regimens used in this study add some heterogeneity to the treatment strategies. When standardised by weight, our results demonstrate the merit of higher induction dosing, supporting the use of an intravenous [IV] 6 mg/kg induction, as was done in both prospective study and randomised controlled trials. [16, clinicaltrial.gov ID: NCT02968108] The use of therapeutic drug monitoring was recently found to help optimise outcomes of UST in adult CD.[33] Further research is needed to assess the best induction regimen in paediatric CD and the potential utility of drug monitoring.

In conclusion, subcutaneous UST was found to be effective in inducing remission in 38% and achieving a response in another 48% of a cohort of paediatric patients with CD refractory to anti-TNF therapy. Over the course of therapy, there was an improvement in clinical activity scores, biochemical markers of disease activity, and growth parameters. This medication was well tolerated overall, and serious adverse events were rare. Based on the results of this study, subcutaneous UST administration should be considered a viable and effective therapeutic option for paediatric patients who are refractory to traditional biologicals.

Funding

None.

Conflict of Interest

PJ has served as a consultant for AbbVie and Janssen and on advisory board for Ferring. CD has served on the advisory board for AbbVie and Janssen. EGS received research support, and served on the advisory boards and speakers' bureau, for AbbVie and Janssen. KJ has received research support and served on advisory boards and speakers' bureau for AbbVie and Janssen. SL served on advisory boards for AbbVie and Janssen. CC was awarded an Advanced IBD Fellowship by Janssen Canada. The other authors have no conflict of interest to disclose.

Author Contributions

MC, CM-V, and LH performed data collection, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. CC performed data collection and reviewed and revised the manuscript. NK performed advanced statistical analyses and participated in the revision of the manuscript. SL, KJ, J-PH, JV, and CD reviewed and revised the manuscript. PJ was involved in study design, coordinated and supervised the data collection, helped carry out the analyses, and reviewed and revised the manuscript. EGS was involved in study design and reviewed and revised the manuscript. All authors approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

References

1. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. *JAMA Pediatr* 2015;**169**:1053–60.
2. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012;**61**:1619–35.
3. Reinink AR, Lee TC, Higgins PD. Endoscopic mucosal healing predicts favorable clinical outcomes in inflammatory bowel disease: a meta-analysis. *Inflamm Bowel Dis* 2016;**22**:1859–69.
4. Hyams J, Crandall W, Kugathasan S, et al.; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;**132**:863–73; quiz 1165–6.
5. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012;**143**:365–74.e2.
6. Sprakes MB, Ford AC, Warren L, Greer D, Hamlin J. Efficacy, tolerability, and predictors of response to infliximab therapy for Crohn's disease: a large single-centre experience. *J Crohns Colitis* 2012;**6**:143–53.
7. Hanauer SB, Feagan BG, Lichtenstein GR, et al.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
8. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**:644–59; quiz 660.
9. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol* 2009;**104**:760–7.
10. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011;**33**:987–95.
11. Sandborn WJ, Feagan BG, Fedorak RN, et al.; Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008;**135**:1130–41.
12. Sandborn WJ, Gasink C, Gao L-L, et al. *Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease*. Waltham, MA: Massachusetts Medical Society; 2012;**367**:1519–28.
13. Feagan BG, Sandborn WJ, Gasink C, et al.; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;**375**:1946–60.
14. Sandborn WJ, Rutgeerts P, Gasink C, et al. Long-term efficacy and safety of ustekinumab for Crohn's disease: results from Im-Uniti long-term extension through two years. *Gastroenterology* 2017;**152**:S585.
15. Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol* 2015;**73**:594–603.
16. Fusillo SJ, Chang V, Stein RE, et al. Ustekinumab responders versus non-responders in refractory pediatric inflammatory bowel disease. *Gastroenterology* 2018;**154**:S82.
17. Rinawi F, Rosenbach Y, Assa A, Shamir R. Ustekinumab for resistant pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2016;**62**:e34–5.
18. Bishop C, Simon H, Suskind D, Lee D, Wahbeh G. Ustekinumab in pediatric Crohn disease patients. *J Pediatr Gastroenterol Nutr* 2016;**63**:348–51.
19. Cameron FL, Garrick V, Russell RK. Ustekinumab in treatment of refractory paediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2016;**62**:e30.
20. 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.
21. Saverymuttu SH, Hodgson HJ, Chadwick VS, Pepys MB. Differing acute phase responses in Crohn's disease and ulcerative colitis. *Gut* 1986;**27**:809–13.
22. Wils P, Bouhnik Y, Michetti P, et al.; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif. 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**:242–50.e1–2.
23. Ma C, Fedorak RN, Kaplan G, et al. Ustekinumab is effective for inducing clinical, endoscopic, and radiographic response and remission in refractory moderate-to-severe Crohn's disease: a multicentre cohort study. *Gastroenterology* 2017;**152**:S410–1.
24. Kopylov U, Afif W, Cohen A, et al. Subcutaneous ustekinumab for the treatment of anti-TNF resistant Crohn's disease—the McGill experience. *J Crohns Colitis* 2014;**8**:1516–22.
25. Harris KA, Horst S, Gadani A, et al. Patients with refractory Crohn's disease successfully treated with ustekinumab. *Inflamm Bowel Dis* 2016;**22**:397–401.
26. 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. *Aliment Pharmacol Ther* 2017;**45**:1232–43.
27. Ma C, Fedorak RN, Kaplan GG, et al. Long-term maintenance of clinical, endoscopic, and radiographic response to ustekinumab in moderate-to-severe Crohn's disease: real-world experience from a multicenter cohort study. *Inflamm Bowel Dis* 2017;**23**:833–9.
28. Deepak P, Loftus EV Jr. Ustekinumab in treatment of Crohn's disease: design, development, and potential place in therapy. *Drug Des Devel Ther* 2016;**10**:3685–98.
29. Lebwohl M, Leonardi C, Griffiths CE, et al. Long-term safety experience of ustekinumab in patients with moderate-to-severe psoriasis [Part I of II]: results from analyses of general safety parameters from pooled Phase 2 and 3 clinical trials. *J Am Acad Dermatol* 2012;**66**:731–41.
30. Wenk KS, Claros JM, Ehrlich A. Flare of pustular psoriasis after initiating ustekinumab therapy. *J Dermatolog Treat* 2012;**23**:212–4.
31. Caca-Biljanovska N, V'lckova-Laskoska M, Laskoski D. Successful management of ustekinumab-induced pustular psoriasis without therapy discontinuation. *Acta Dermatovenerol Croat* 2013;**21**:202–4.
32. Hay RA, Pan JY. Paradoxical flare of pustular psoriasis triggered by ustekinumab, which responded to adalimumab therapy. *Clin Exp Dermatol* 2014;**39**:751–2.
33. 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**:1427–34.e2.