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Safety and Potential Efficacy of Escalating Dose of Ustekinumab in Pediatric Crohn Disease (the Speed-up Study): A Multicenter Study from the Pediatric IBD Porto Group of ESPGHAN

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ABSTRACT

Objectives: Escalation of the ustekinumab (UST) maintenance dosage was effective in adults with Crohn disease (CD), but no data are available for children. We evaluated the effectiveness and safety of dose escalation of UST in pediatric CD.

Methods: This was a retrospective multicenter study from 25 centers affiliated with the IBD Interest and Porto groups of ESPGHAN. We included children with CD who initiated UST at a standard dosing and underwent either dose escalation to intervals shorter than 8 weeks or re-induction of UST due to active disease. Demographic, clinical, laboratory, endoscopic, imaging, and safety data were collected up to 12 months of follow-up.

Results: Sixty-nine children were included (median age 15.8 years, interquartile range 13.8–16.9) with median disease duration of 4.3 years (2.9–6.3). Most children were biologic (98.6%)- and immunomodulator (86.8%)- experienced. Clinical response and remission were observed at 3 months after UST escalation in 46 (67%) and 29 (42%) children, respectively. The strongest predictor for clinical remission was lower weighted Pediatric Crohn Disease Activity Index (wPCDAI) at escalation ($P = 0.001$). The median C-reactive protein level decreased from 14 (3–28.03) to 5 (1.1–20.5) mg/L ($P = 0.012$), and the fecal calprotectin level from 1100 (500–2300) to 515 (250–1469) μg/g ($P = 0.012$) 3 months post-escalation. Endoscopic and transmural healing were achieved in 3 of 19 (16%) and 2 of 15 (13%) patients, respectively. Thirteen patients (18.8%) discontinued therapy due to active disease. No serious adverse events were reported.

Conclusions: Two-thirds of children with active CD responded to dose escalation of UST. Milder disease activity may predict a favorable outcome following UST dose escalation.

An infographic is available for this article at: *http://links.lww.com/MPG/C933*.

Key Words: biologics, children, Crohn disease, ustekinumab

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What Is Known

- Ustekinumab (UST) is an effective therapy for inflammatory bowel disease (IBD).
- Escalation of the UST maintenance dosage may be effective in adults with Crohn disease (CD) who did not respond to the standard dose.

What Is New

- The clinical response and remission rates at 3 months after UST escalation in children with CD were 67% and 42%, respectively.
- The C-reactive protein and fecal calprotectin levels decreased significantly during the 12 months follow-up.
- No serious adverse events were reported.
- UST dose escalation may be considered in children with CD who experience insufficient response to the standard dose.

Ustekinumab (UST; Stelara®, Janssen Pharmaceuticals) was found to be effective for the induction and maintenance of remission in adult Crohn disease (CD) (1,2) and ulcerative colitis (3,4). The standard UST treatment regimen includes an intravenous (IV) induction dose followed by subcutaneous (SC) maintenance dosing administered every 8 or 12 weeks (1,2). A benefit in achieving endoscopic response was observed in the former regimen (5). Dose escalation by shorter intervals in adults with CD who failed to respond to the standard UST protocol was shown to be effective

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(6–10). In a multicenter study, Kopylov et al (8) showed that over 50% of refractory patients responded to an escalation of the UST dosage, and that 40% achieved clinical remission. An improvement in inflammatory markers was also observed (9,10).

The uSTEkinumab use in paediatric Crohn disease (11) multicenter study from the Porto group of ESPGHAN is the largest real-life cohort of UST therapy in pediatric CD, and it showed similar effectiveness of UST as reported in adults. Several additional studies described the effectiveness of UST in pediatric CD and addressed the influence of the dosing regimen (12–14). Dayan et al (12) reported a need to interval shortening in 62% of the patients, and Chavannes et al (13) showed that a higher induction dose was associated with a lower discontinuation rate. Importantly, no pediatric study has thus far defined UST dose escalation as its primary outcome.

We, therefore, aimed to investigate the impact of dose escalation of UST in pediatric CD in terms of the effectiveness and safety.

METHODS

Study Design and Population

This was a retrospective cohort study from centers affiliated with the Pediatric IBD Interest and Porto groups of ESPGHAN. Children (<18 years of age) diagnosed with CD according to the revised Porto criteria (15), who started on the standard UST dosing every 8 or 12 weeks, and underwent dose escalation to shorter intervals than every 8 weeks or re-induction of UST due to active disease were included. The standard UST dosing in children includes a first IV dose of 6 mg/kg rounded to 130 mg (a maximum dose of 520 mg). SC dosing usually starts at week 8, with a body surface area-adjusted to adult dose of 90 mg every 8 weeks (16). Active disease was defined as weighted Pediatric Crohn Disease Activity Index (wPCDAI) ≥12.5 (17). Failure of standard dosing of UST was defined as insufficient clinical response (wPCDAI >12.5) or abnormal fecal calprotectin (FC) or serum C-reactive protein (CRP) levels. All patients had at least 3 months of follow-up after UST escalation.

Data Collection

We collected demographic and clinical data that included CD characteristics according to the Paris classification (18), disease activity as measured by wPCDAI, concomitant therapy, disease exacerbations, surgeries, CD complications (including strictures and fistulizing disease), laboratory results, imaging findings, and the results of endoscopy when performed. Any adverse events that were potentially related to therapy according to the judgment of the treating physician were recorded. The data were collected at diagnosis of CD, at the beginning of UST therapy, at UST dose escalation, and at 3, 6, and 12 months thereafter. Clinical remission and mild, moderate, and severe disease were defined as wPCDAI <12.5, 12.5–40, 42.5–57.5, and >57.5, respectively.

Outcomes

The primary outcome was corticosteroid-free and exclusive enteral nutrition (EEN)-free clinical remission at 3 months following dose escalation. Secondary outcomes were corticosteroid-free and EEN-free clinical remission at 6 and 12 months, clinical response at 3, 6, and 12 months (a decline in the wPCDAI of >17.5 points), clinical and laboratory remission at 3, 6, and 12 months, reduction of CRP to levels <5 mg/L and FC to levels <150 μg/g, endoscopic remission (defined as a complete normalization of the SES-CD (19) verified at colonoscopy), transmural healing [defined as radiological global assessment of complete remission at bowel ultrasound or magnetic resonance enterography (MRE)], and adverse events of following escalation. Active perianal disease was defined as an active fistula, drainage, tenderness, or abscess.

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The data underlying this article will be shared on reasonable request to the corresponding author.

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Statistical Analyses

Categorical variables were presented as frequency and percentage. Continuous variables were evaluated for normal distribution with histograms and Q–Q plots and expressed as median and interquartile range (IQR). Categorical variables were compared by the Chi-square test or Fisher's exact test, as appropriate, while continuous variables were compared by the Mann-Whitney test. All analyses were done in the intention-to-treat (ITT) population. Children that discontinued UST therapy were considered treatment failures and were imputed for nonresponse. For 33 children that did not complete 6 months of follow-up data were carried forward from the 3 months observation (last observation carried forward). A logistic regression model was sought for exploring predictors for the studied outcomes. A log-rank test was used to study the association between categorical variables and discontinuation of therapy, while Cox regression was applied for continuous variables. The multivariate analysis included variables that were associated with the outcome with a P value <0.1. All the statistical tests were 2-sided, and a P value <0.05 was considered statistically significant. SPSS was used for all statistical analysis (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Ethics Committee Approval

This study was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center (TLV-20-0705) and equivalent committees of all contributing centers.

RESULTS

Sixty-nine children from 25 centers were included in the study, 33 (47.8%) of whom were males (Table 1). Before the initiation of UST therapy, 59 (86.8%) had been treated with immunomodulators and 68 (98.6%) with biologic agents, most (44, 64.7%) with more than 1 biologic agent (Table 1). Before UST escalation, 14 (20.3%) children already had demonstrated partial clinical response to UST therapy and 55 (79.7%) were primary non-responders.

The method of escalation in the majority of the patients was interval shortening (63/69, 91.3%), mostly to every 4–6 weeks (Table 2). UST therapy at escalation was provided in combination in 46 (66.7%) children, mostly with immunomodulators (21/46, 45.6%), partial enteral nutrition (20/46, 43.5%), and corticosteroids (15/46, 32.6%). Six (13%) children received combination therapy of UST and another biologic agent (3 infliximab, 2 vedolizumab, and 1 adalimumab). Besides corticosteroids, the combination therapy was overall steady along the study period. Six (13%) children required 2 escalations of UST therapy (from 6 to 4 weeks or re-induction).

CD Outcomes at 3 Months After Escalation

Three months after escalation, clinical response was achieved in 46 (67%) children, and corticosteroid- and EEN-free clinical remission in 29 (42%) children (Fig. 1). The median wPCDAI decreased from 35 (20–45) to 15 (7.5–27.5; $P < 0.001$; Fig. 2A). The median CRP level decreased from 14 (3–28) mg/L to 5 (1.1–20.5) mg/L ($P = 0.012$; Fig. 2B). The number of children who had an elevated CRP decreased from 41 (63.1%) to 26 (45.6%; $P = 0.053$). The FC level decreased from 1100 (500–2300) μg/g to 515 (250–1469) μg/g ($P = 0.012$; Fig. 2C). The rate of an elevated FC (>150 μg/g) dropped from 92.4% to 82.2% ($P = 0.124$). Using a cut-off of 250 μg/g, the rate of an elevated FC dropped from 88.6% to 70.5% ($P = 0.064$).

While the rates of clinical response after 3 months were similar between children with mild, moderate, and severe disease

TABLE 1. Demographic and clinical characteristics of the study cohort ($n = 69$)

	$n = 69$
Age at diagnosis of CD, y	10.9 (7.8–12.5)
Male sex	33 (47.8%)
Ethnicity	
Caucasian	61 (88.4%)
Non-Caucasian	8 (11.6%)
Family history of IBD	14 (20.3%)
Disease location	
L1	16 (23.2%)
L2	21 (30.4%)
L3	32 (46.4%)
L4	33 (47.8%)
Disease behavior	
B1	42 (60.9%)
B2	13 (18.8%)
B3	14 (20.3%)
Perianal disease	16 (23.2%)
Growth*	
G0	44 (63.8%)
G1	25 (36.2%)
Extraintestinal manifestations	11 (15.9%)
Disease activity at diagnosis†	
Mild	19 (29.2%)
Moderate	27 (41.5%)
Severe	19 (29.2%)
Therapy before UST	
EEN	35 (51.5%)
PEN	16 (23.5%)
CDED	10 (7.1%)
Corticosteroids	44 (64.7%)
5-ASA	28 (41.2%)
Thiopurines	51 (75%)
Methotrexate	32 (47.1%)
Infliximab	54 (79.4%)
Adalimumab	51 (75%)
Vedolizumab	14 (20.6%)
Antibiotics	15 (21.7%)
Thalidomide	6 (8.7%)
Surgery	14 (20.3%)
Ileocecal resection	11 (15.9%)
Colectomy	3 (4.3%)
Number of previous biologic agents	
None	1 (1.5%)
1	23 (33.8%)
2	36 (52.9%)
3	8 (11.8%)
Previous immunomodulator therapy	59 (86.8%)

5-ASA = 5-aminosalicylic acid; CD = Crohn disease; CDED = Crohn disease exclusion diet; EEN = exclusive enteral nutrition; IBD = inflammatory bowel disease; PEN = partial enteral nutrition; UST = ustekinumab; wPCDAI = weighted pediatric Crohn disease activity index. *G0: no evidence of growth delay. G1: growth delay. †According to the wPCDAI.

TABLE 2. UST therapy and dose escalation data of the study cohort (n = 69)

UST induction dose, mg/kg	5.8 (5.1–6.3)
UST maintenance dose	
45 mg	11 (15.9%)
90 mg	54 (78.3%)
Other	4 (5.8%)
Frequency of maintenance therapy	
Every 8 wk	67 (97.1%)
Every 12 wk	2 (2.9%)
Duration from UST therapy to escalation, mo	6 (3.6–12)
Age at escalation, y	15.8 (13.8–16.9)
Disease activity at escalation*	
Mild	43 (62.3%)
Moderate	20 (29%)
Severe	6 (8.7%)
Escalation type	
Shortened intervals	63 (91.3%)
Re-induction	3 (4.3%)
Shortened intervals and re-induction	3 (4.3%)
Intervals after escalation	
Every 4 wk	38 (57.6%)
Every 5 wk	2 (3%)
Every 6 wk	24 (36.4%)
Every 7 wk	2 (3%)
Combination therapy during escalation	46 (66.7%)
EEN	2 (4.3%)
PEN	20 (43.5%)
Corticosteroids	15 (32.6%)
5-ASA	6 (13%)
Thiopurines	10 (21.7%)
Methotrexate	11 (23.9%)
Biologic agents	6 (13%)

5-ASA = 5-aminosalicylic acid; EEN = exclusive enteral nutrition; PEN = partial enteral nutrition; UST = ustekinumab; wPCDAI = weighted pediatric Crohn disease activity index. *According to the wPCDAI.

(65%, 70%, and 67%, respectively), more children with mild disease activity achieved clinical remission (53.5% compared to 23.1% children with moderate and severe disease, P = 0.013).

Nine of 13 (69.2%) children who were treated with corticosteroids at baseline could be weaned within 3 months after escalation. Corticosteroids were initiated in 3 children during the follow-up.

CD Outcomes at 6 Months After Escalation

Clinical response was achieved in 39 (57%) and clinical remission in 26 (38%; Fig. 1).

The longitudinal changes in the wPCDAI, CRP, and FC levels are presented in Figure 2. The serum CRP levels decreased from 14 (3–28) mg/L at the initiation of escalation to 4 (1–14.6) mg/L (P = 0.11). While 41 (63.1%) children had an elevated CRP level at the initiation of escalation, only 14 (42.4%) children had an elevated CRP level after 6 months (P = 0.051). The FC

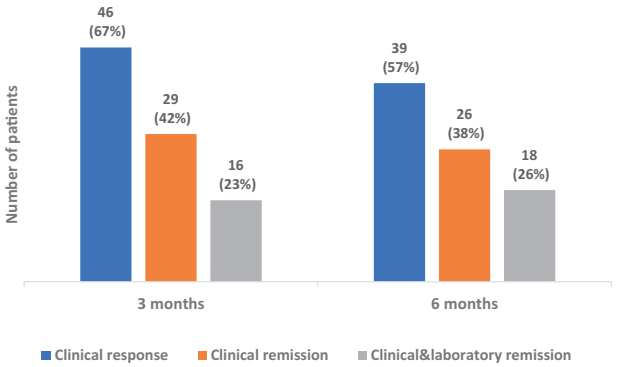

FIGURE 1. The main study outcomes at 3 and 6 mo following UST dose escalation. UST = ustekinumab.

level decreased from 1110 (499–2300) to 453 (238–1100) µg/g (P = 0.025). The rate of an elevated FC level decreased from 92.4% to 86.9% (P = 0.447).

None of 7 children who did not respond at 3 months and continued on escalated therapy subsequently responded at 6 months of dose escalation.

CD Outcomes at 12 Months After Escalation

Twenty children completed a 12 months of follow-up under UST therapy. Thirteen children discontinued UST therapy during the follow-up. Clinical response was achieved in 14/33 (42.4%) children at 12 months [with the exclusion of patients who discontinued UST therapy 14/20 (70%) responded at 12 months]. Clinical remission was achieved in 10 of 33 (30.3%) at 12 months [with the exclusion of patients who discontinued UST therapy 10/20 (50%) achieved clinical remission at 12 months]. Serum CRP levels decreased from 14 (3–28.03) mg/L at escalation to 2.25 (1.38–7.43) mg/L (P = 0.201). While at escalation 41 (63.1%) children had an elevated CRP, only 5 (25%) children had an elevated CRP at 12 months (P = 0.003). FC decreased from 1110 (499–2300) to 248 (118–1159) µg/g (P =0.056). The rate of an elevated FC decreased to 66.7% after 12 months of dose escalation (P = 0.007).

Complete endoscopic remission was reported in 3 of 19 (16%) children at the end of the follow-up (23% of the responders, 4.3% of the ITT population). Transmural healing was reported in 2 of 15 (13%) children (18% of the responders, 2.9% of the ITT population).

Predictors of Outcomes

The predictors of the main study outcome are presented in Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C931*. A multivariate analysis that included the wPCDAI, hemoglobin, CRP, and albumin levels revealed that the wPCDAI at escalation was a significant predictor of clinical remission at 3 months afterwards [odds ratio (OR) 0.955, confidence interval (CI) 0.917–0.995), P = 0.027]. The wPCDAI at the diagnosis of CD was a significant predictor of clinical response at 3 months after escalation [OR 0.962 (CI 0.932–0.993), P = 0.015]. There was no association between the study outcomes and age, CD duration, phenotype, previous therapy, combination therapy, intervals after escalation and response to UST before escalation.

Perianal CD

Eight children had an active perianal disease at the initiation of UST escalation. Four (50%) children achieved a complete clinical remission in their perianal disease.

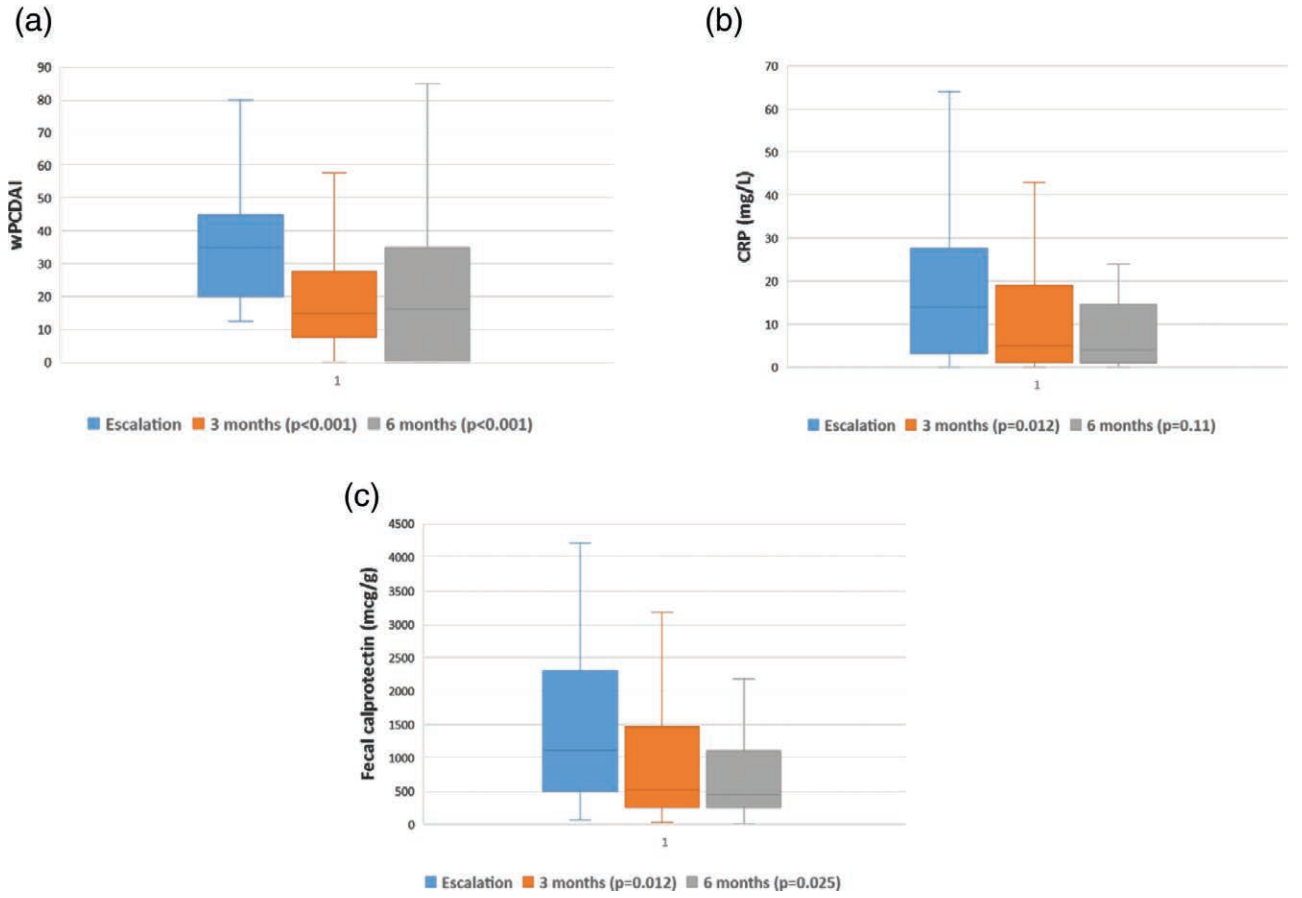

FIGURE 2. Change in wPCDAI (A), CRP (B), and FC (C) following UST dose escalation. CRP = C-reactive protein; FC = fecal calprotectin; UST = ustekinumab; wPCDAI = weighted Pediatric Crohn's Disease Activity Index.

Discontinuation of UST Therapy

Thirteen (18.8%) children discontinued UST therapy, at a median duration of 3 (IQR 3–4) months (Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/C932*). All children discontinued therapy due to active disease. Risk factors for discontinuation were penetrating CD phenotype ($P = 0.007$) and extraintestinal manifestations ($P = 0.005$).

Adverse Events

Adverse events that were potentially related to therapy were reported in 6 (8.7%) children, and included infections (cellulitis, external otitis), arthritis, flushing, mild leukopenia, and fever. All adverse events were mild, and none of the children has stopped therapy due to adverse events.

DISCUSSION

UST is becoming a common second- and third-line biologic therapy for pediatric CD, and this study is the first whose primary outcome was to evaluate the effectiveness and safety of UST dose escalation in children. We hypothesized that our cohort of children with refractory CD who had insufficient response to standard maintenance dosing may benefit from dose escalation. Our results demonstrated that 67% achieved clinical response and that 42% achieved clinical remission within 3 months after dose escalation.

UST is currently not Food and Drug Administration-approved as therapy for pediatric CD and only data from phase 1 study have been published (20). In real life, however, UST is used in refractory cases (11–14). Treatment discontinuations due to primary and secondary nonresponse are frequent in inflammatory bowel disease (IBD). A strategy to overcome nonresponse to UST among children with CD has not been established. Considering that the children in our cohort were refractory to many other therapies, dose escalation of UST emerged as next in line therapeutic option. The clinical benefit of dose escalation is thought to be mediated through increase in drug levels. Serum concentrations of UST were shown to be proportional to dose, and associated with clinical efficacy and endoscopic remission in adult CD (1,21–23).

The median duration of UST therapy before escalation in our cohort was 6 months, similar to the durations reported in adult studies (6,8–10). Clinical response was achieved in 67% and corticosteroid- and EEN-free clinical remission was achieved in 42% of our cohort at 3 months after escalation. Moreover, the wPCDAI, the CRP, and FC levels decreased significantly. These results are in line with those of Kim et al (14) who studied the largest real-life pediatric cohort published to date. They reported a decline of abbreviated PCDAI from 25 to 5 and an increase in the clinical remission rate from 11% to 61%. Their study, however, failed to show any significant change in serum CRP following dose escalation. Our results are also in line with adult CD studies that reported response rates of 50%–60% and remission rates of 30%–40% after dose escalation (1,6,8,9,24,25). A meta-analysis that included 15 studies showed a clinical response rate of 55% after UST dose escalation (26). Those studies and others have also demonstrated laboratory

responses, with a decrease or normalization of CRP levels in 20% of the patients (6,8,9) and a decrease in FC values following escalation (9,21). As in other studies (8), we observed a high rate (69%) of corticosteroid discontinuation within 3 months after escalation. It should be mentioned that several other studies have reported a lower probability (35%–47%) to wean off corticosteroids (6,9–10).

While the short-term effect of UST dose escalation has been well studied among adults with CD, the longer-term outcome of the patients is less certain. In our study, clinical response was achieved in 57% and the rates of clinical remission were 38% at 6 months since escalation. The clinical response and remission rates at 12 months were 42% and 30%, respectively. Various rates were reported in 3 adult studies. Kopylov et al (8) observed a response rate of 52% and a clinical remission rate of 42% after a follow-up of 26 weeks, while Fumery et al (6) reported a lower rate (26%) of clinical remission after a median follow-up of 8.2 months, and Haider et al (10) observed long-term response and remission rates of 33% and 13%, respectively. The mild but consistent decrease of the response rates after 6 and 12 months may imply loss of response over time in patients who initially responded to dose escalation. This may reflect the annual risk of loss of response to UST of approximately 20% in the general IBD population (26).

Importantly, none of 7 children of our study who did not respond at 3 months and continued UST therapy did respond at 6 months. These results are in line with those of Kopylov et al (8), who observed that only 20% of the patients who did not respond at week 16 responded later on. Based on these results, we conclude that in most of the cases, a 3-month trial of dose escalation is sufficient to predict response.

There are currently no data for identifying the patients that are more likely to benefit from dose escalation of UST. Several studies and a meta-analysis failed to find any factors that were associated with a likelihood of response (6,8,27). In their univariate analysis, Fumery et al (6) observed that loss of response to UST (compared to incomplete response) and longer duration of UST therapy before dose intensification were associated with clinical response. Dalal et al (25) showed that perianal disease, high Harvey-Bradshaw Index, and opioid use were associated with failure to achieve remission. The principal predictor of a response in our cohort was lower disease activity. Specifically, lower wPCDAI at escalation was a significant and independent predictor of achieving clinical response and remission at 3 months after escalation. While the univariate analysis revealed that shortening intervals (compared to re-induction) was a predictor of clinical response after 3 months, this finding was not significant in the multivariate analysis. Several other factors, such as the absence of perianal involvement, milder disease activity, and lower erythrocyte sediment rate, however, were found to be predictors of longer-term outcome.

Dose escalation of UST may improve endoscopic scoring (9) and induce endoscopic remission, which was reported in 9%–36% (6,8,21) of adult cases, a range in which our rate of 27% falls. In their meta-analysis, Meserve et al (27) reported that 61% of the patients were able to achieve endoscopic response, including 29% who achieved endoscopic remission following dose escalation. That low rate of endoscopic remission correlates with the low rate of FC normalization in our study and in those of others, as well as with our low rate (13%) of transmural healing.

We observed a relatively high rate (50%) of remission of perianal disease after dose escalation of UST. Similar remission rates were observed in other studies (6,8,9). Importantly, 4 (5.8%) children in our study group sustained a new perianal disease, and 4 (5.8%) required intestinal resection during the follow-up. These events are compatible with reports of the higher rates of surgery in the adult CD population after escalation (6,8).

The main reason for UST withdrawal after dose escalation was reportedly the absence of response (6,9), and this was reflected by the observation that all children in our cohort who discontinued UST therapy had a persistent active disease. We identified several risk factors for the discontinuation of UST therapy after escalation, such as penetrating disease and extraintestinal manifestations.

The safety profile of UST is generally favorable. In a pooled safety analysis of results from phase 2/3 studies conducted by Sandborn et al (28), the safety was comparable to placebo. In line with other studies that evaluated adverse events after UST escalation (6,8,9,14,27), adverse events were sustained by only a few of our children: most were mild and none resulted in the discontinuation of therapy.

The study has some limitations. The pharmacokinetics of UST could not be assessed due to its retrospective design. Although no correlation was observed between serum UST concentrations and clinical outcome in pediatric population (20), previous studies in adults have shown that serum concentrations of UST were associated with clinical efficacy and endoscopic remission (21–23). Another limitation is the lack of standardized endoscopic and radiologic follow-up for all patients. Due to the limited availability of objective endoscopic and radiologic data, most of the study outcomes were based on clinical measures. However, other parameters of effectiveness that we used were objective, such as serum and fecal inflammatory markers and the extent of transmural and endoscopic healing for part of the patients. The median age of 15.8 (13.8–16.9) years at dose escalation may limit the applicability of the conclusions to a younger population.

CONCLUSIONS

In conclusion, our findings suggest that UST dose escalation may be considered in children with CD who experience loss of response or insufficient response to the standard UST dose. We showed that UST dose escalation resulted in improvement in both clinical and biological markers comparable to adult study findings. Further studies should investigate which populations of CD patients are most likely to achieve a therapeutic benefit from UST escalation and thereby increase clinical response and improve disease outcome.

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