



Effectiveness of ustekinumab dose escalation in Crohn's disease patients with insufficient response to standard-dose subcutaneous maintenance therapy

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Summary

Background: Ustekinumab is effective in Crohn's disease. However, a substantial proportion of patients will not respond or lose response to ustekinumab. The current evidence to support the effectiveness of dose-optimisation for ustekinumab nonresponse is limited.

Aim: To assess the effectiveness of dose escalation of ustekinumab.

Methods: This was a multicentre retrospective cohort study. We included active Crohn's disease patients who received a standard-dose intravenous induction and at least one subcutaneous ustekinumab 90 mg dose. All enrolled patients received dose escalation by either shortening the interval between the doses to every 4 or 6 weeks, intravenous reinduction or a combination of strategies. The primary outcome of the study was clinical response at week 16 after dose escalation.

Results: A total of 142 patients (22 centres/14 countries) were included. The patients were dose-escalated after a median treatment duration of 30 weeks. At week 16 from escalation, 73/142 (51.4%) responded to treatment, including 55/142 (38.7%) in clinical remission. Corticosteroid-free remission was achieved in 6/34 (17.6%) patients on corticosteroids at the time of escalation; 118/142 (83%) continued treatment beyond week 16. Follow-up data beyond week 16 were available for 74/118 (62.7%) patients. On the last follow-up, 51/98 (52%) patients with available data responded to treatment, including 41/98 (42%) in clinical remission.

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Conclusions: Intensification of ustekinumab maintenance dosage was effective in over 50% of the patients. This strategy should be considered in patients who are nonresponsive to every 8 weeks ustekinumab maintenance dosing.

1 | INTRODUCTION

Ustekinumab (UST) is a monoclonal antibody that targets the p40 subunit of interleukin (IL) 12 and 23. UST is effective for treatment of Crohn's disease (CD) and ulcerative colitis.¹⁻⁴ In addition to randomised controlled trials, multiple real-world studies corroborated the effectiveness of UST in the treatment of CD.⁵⁻¹⁹ However, the risk of primary and secondary loss of response to UST has not been extensively reported. In the recently published long-term extension of the UNITI trials, clinical remission was well maintained from week 44 to 92 for both every 12 weeks (q12w) (77.4%/72.6%) and every 8 weeks (q8w) regimen (84.1%/74.4%).³ Nevertheless, the rates of sustained response appear to be lower in the real-world setting. In a multicentre real-world study from the Netherlands, the probability of remaining on ustekinumab treatment at 52 weeks was 62.9%.⁷ Similar results were reported in a recent Belgian cohort study.¹³

The vast majority of CD patients treated with ustekinumab in the real-world setting have failed at least two previous biologics.⁹ Additional therapeutic options in these patients are severely limited. Therefore, there is a need for an effective strategy for management of nonresponse to ustekinumab.

The standard ustekinumab treatment regimen for CD includes an intravenous (IV) induction (adjusted 6 mg/kg dose) followed by UST subcutaneous (SC) 90 mg administered every 12 or 8 weeks. No significant differences between both dose regimens with regards to clinical efficacy were demonstrated in the UNITI trials.^{2,3} However, every 8 weeks regimen (q8w) was more effective in achieving endoscopic response.¹ Dose escalation q8w in patients failing to respond to q12w regimen has been shown to be effective.^{3,20} Yet, there are scarce data to support efficacy of further dose escalation in patients failing q8w dosing. In a Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) cohort study, published as a conference report, clinical response was obtained in 43/69 (57.1%) of the patients after 2.1 months post every 4 weeks (q4w) optimisation.²¹ In addition, successful intravenous reinduction was described in a case series of three patients with either primary or secondary nonresponse to UST.²²

Additional data to support a dose-escalation regimen in CD patients failing to respond to ustekinumab are required. The aim of the present study was to evaluate the effectiveness and safety of dose escalation of UST in patients who did not respond or lost response to ustekinumab q8w maintenance dose.

2 | METHODS

This was a multicentre retrospective cohort study. The protocol was reviewed and approved by the Clinical committee of the European

Crohn's and Colitis organisation (ECCO). The cohort study included active (defined as Harvey-Bradshaw Index (HBI) ≥ 5 or Crohn's disease activity index (CDAI) ≥ 150) CD patients. The included patients received at least two doses of ustekinumab (IV induction of 6 mg/kg followed by SC 90 mg injection) and were either dose-escalated to q4w or q6w or, alternatively, received an IV reinduction (6 mg/kg) instead of a scheduled SC dose or a combination of IV and SC escalation. Patients without active disease as per CDAI/HBI, and patients with pouch or ostomy were excluded from the study. Patients who started q12w maintenance after IV induction could be included in the study only if they were escalated to q8w regimen prior to further escalation.

The primary objective of the study was clinical response ($\Delta\text{HBI} \geq 3$ or $\Delta\text{CDAI} \geq 70$) at week 16 from the escalation. Secondary outcomes included clinical remission (HBI ≤ 4 ; CDAI ≤ 150) at week 16; C-reactive protein (CRP) normalisation (as per cut-off levels used in the corresponding institutions) at week 16 (in patients with elevated CRP at the time of escalation); steroid-free clinical remission at week 16 (in patients receiving systemic corticosteroids at the time of escalation) and steroid-free clinical response at week 16. In addition to week 16 from the escalation, we addressed long-term outcomes (last visit after week 16, up to 52 weeks from dose escalation) when available. Last follow-up secondary outcomes included clinical response and remission, steroid-free response and remission, improvement in perianal fistula drainage or fistula healing (based on physician's assessment or per imaging where available). We also collected safety outcomes including patient-reported adverse events, serious adverse events (resulting in hospitalisation or treatment discontinuation), hospitalisations and CD-related surgery following dose escalation.

3 | STATISTICAL METHODS

Descriptive statistics were presented as means \pm standard deviations (SD) for parametric variables, medians with interquartile ranges (IQR) for nonparametric continuous variables and percentages for categorical variables. Categorical variables were analysed by chi-square/Fisher's exact test and continuous variables by *t* test/Mann Whitney test as appropriate. A two-tailed $P < 0.05$ was considered statistically significant. We constructed a multivariate logistic regression model to identify the independent predictors of ustekinumab discontinuation at week 52. Variables with significance level < 0.1 on the univariate analysis were included in the model. To investigate the effect of the variables on duration of continued UST treatment, we performed a survival analysis, Kaplan-Meier survival curve and Cox multivariate proportional hazard model. The model included variables with significance level < 0.1 on univariate analysis. We used IBM SPSS statistical (Version 20.0) in performing the analysis. Ethical approval was obtained as per the requirements of each of the participating centres.

4 | RESULTS

One hundred and forty-two patients from 22 centres in 14 countries (13 Europe and 1 Canada) were included in the study. The clinical and demographic characteristics of the patients are detailed in Table 1. Only 3.5% of the patients were biologic-naïve, 23.2% received one prior biologic, 39.4% received two prior biologics, 32.4% received three prior biologics and 1.4% received four prior biologics. Fifty-seven (40%) of the patients had previously received both anti-TNFs and vedolizumab. One hundred and six (77%) had elevated CRP at dose escalation. All patients received intravenous UST induction and SC maintenance (90 mg SC q8w); 9/142 (6.3%) received q12w and were escalated to q8w before inclusion in the study. The mean duration of SC maintenance therapy before dose escalation was 29 (IQR 18-46) weeks with a median of four (IQR 2-6) injections. All patients had active CD (median HBI- 8 (IQR 6-12) at the time of dose escalation.

Ninety-one (64.1%) of the patients were escalated to q4w regimen, 20/142 (14.1%) patients were escalated to q6w, 14/142 (9.9%) patients received an IV reinduction and 17/142 (12%) a combination of IV reinduction and interval shortening.

5 | TREATMENT OUTCOMES

5.1 | Week 16 from escalation

Clinical response was achieved by 73/142 (51.4%) patients, including 55/142 (38.7%) patients in clinical remission. CRP normalised in 21/98 (21.4%) patients with CRP values available at both time points. Systemic corticosteroids were discontinued in 23/34 (67.6%) patients who were on corticosteroids at the time of escalation. Corticosteroid-free remission was achieved by 6/34 (17.6%) patients on corticosteroids upon escalation. Corticosteroid treatment was started by 6/108 (5.6%) patients who were not treated with corticosteroids upon dose escalation.

The likelihood of achieving clinical remission was similar between patients who received intravenous reinduction vs those who received SC interval shortening (Table 2). None of the clinical or demographic parameters were associated with likelihood of response (Table 2). Ustekinumab was discontinued by 24 (17%) of the patients due to clinical nonresponse (17/91 (18.7%) patients who escalated to q4w, 1/20 (5%) patients escalated to q6w, 5/14 (35.6%) patients who received IV reinduction and 1/17 (5.9%) patients who received both IV reinduction and SC escalation respectively).

5.2 | Maintenance

Clinical follow-up beyond week 16 was available for 74/118 (62.7%) patients who continued treatment (median duration of follow-up was 26 (IQR 32-52) weeks); 44 patients did not have follow-up data available beyond week 16. Maintenance

TABLE 1 Clinical and demographic characteristics of the included patients

Age at treatment onset, years (median, interquartile range)	35 (26-49)
Disease duration (median, interquartile range)	10 (5-17)
Gender (n, %)	
Male	55 (38.7%)
Female	87 (61.3%)
Behaviour (n, %)	
Nonstricturing nonpenetrating	51 (35.9%)
Stricturing	53 (37.3%)
Penetrating	38 (26.8%)
Smoking (n, %)	
Never	101 (70.9%)
Active smoker	20 (14.2%)
Past smoker	21 (14.9%)
CD location (n, %)	
Small bowel	25 (17.6%)
Colon	31 (21.8%)
Small bowel and colon	86 (60.6%)
History of perianal disease (n, %)	56 (40.1%)
History of previous abdominal surgery (n, %)	81 (57%)
Active perianal disease at escalation (n, %)	33 (23.2%)
Number of previous biologic therapies (n, %)	
Previous biologics (n, %)	
None	5 (3.5%)
1	33 (23.2%)
2	56 (39.4%)
3	46 (32.4%)
4	2 (1.4%)
Elevated CRP (n, %)	106 (77.4%)
Systemic corticosteroids at escalation (n, %)	34 (24%)
Concomitant immunomodulators at escalation (n, %)	24 (16.9%)

Abbreviations: CD, Crohn's disease; CRP, C-reactive protein.

outcomes were reported for patients who had available data beyond week 16 or discontinued treatment by week 16 (n = 98) (Figures 1 and 2). At last follow-up, 51/98 (52%) patients responded to treatment, including 41/98 (42%) who achieved clinical remission (with the exclusion of patients who discontinued ustekinumab by week 16, 51/74 (68.9%) responded including 41/74 (55.4%) who achieved clinical remission). Eleven of 53 (20.7%) patients who did not respond at week 16 and had available maintenance data responded subsequently, including 9/54 (17%) who achieved clinical remission. Corticosteroid-free remission was achieved by 9/34 (26.5%) patients who were treated with corticosteroids at dose escalation (including six patients who had achieved corticosteroid-free remission by week 16 as described above). Corticosteroids were initiated in two additional patients after week 16; overall, 8/108 (7.4%)

TABLE 2 Variables associated with week 16 response

	Week 16 response				P
	no (n = 69)		yes (n = 73)		
	n	%	n	%	
Age at treatment onset, years (median interquartile range)	34	(25-44)	37	(27-50)	0.25
Gender (n, %)					
Male	22	31.9%	33	45.2%	0.1
Female	47	68.1%	40	54.8%	
CD location (n, %)					
Small bowel	12	17.4%	13	17.8%	0.99
Colon	15	21.7%	16	21.9%	
Small bowel and colon	42	60.9%	44	60.3%	
Behaviour (n, %)					
Nonstricturing nonpenetrating	24	34.8%	27	37.0%	0.2
Stricturing	22	31.9%	31	42.5%	
Penetrating	23	33.3%	15	20.5%	
Smoking (n, %)					
Never	51	75.0%	49	67.1%	0.5
Active smoker	9	13.2%	11	15.1%	
Type of escalation					
Past smoker	8	11.8%	13	17.8%	0.48
Q4w	43	62.3%	48	65.8%	
Q4w + IV reinduction	6	8.7%	10	13.7%	
Q6w	11	15.9%	10	13.7%	
IV reinduction	9	13.0%	5	6.8%	
Elevated CRP (n, %)	56	82.1%	52	72.9%	0.2
Systemic corticosteroids at escalation (n, %)	20	29.0%	15	20.5%	0.7
Concomitant immunomodulators at escalation (n, %)	12	17.4%	12	16.4%	0.9

Abbreviations: CD, Crohn's disease; CRP, C-reactive protein; IV, intravenous; Q4w- every 4 weeks; Q6w, every 6 weeks.

patients who were not on corticosteroids upon dose escalation were started on corticosteroids throughout the duration of the follow-up. Sixty-seven (68.4%) patients continued ustekinumab treatment at last follow-up.

Kaplan-Meier curve for discontinuation-free survival appears on Figure 3. None of the clinical or demographic parameters, including the escalation strategy, was significantly associated with the duration of drug discontinuation-free survival (data not shown).

Endoscopic evaluation both before (within 4 weeks) escalation and after escalation (24 (IQR 16-32) weeks from escalation) was available for 23 patients. Mucosal healing was reported for 2/23 (8.6%) patients. An endoscopic improvement was reported for 11 (47.8%) of 23 patients and no improvement for 10 (43.4%) of 23 patients.

Of 33 patients with active perianal disease, improvement was reported by 14 (42.4%) patients at week 16. Out of 17 patients with

active perianal disease (and available data) beyond week 16, improvement was reported by 11 (64.7%) patients.

6 | SAFETY

Adverse events followed escalation were reported by 11 (7.7%) of the 142 patient and included skin eruptions (two patients), upper respiratory tract infection that required hospitalisation and subsequent treatment discontinuation (one patient), acute gastroenteritis of unknown aetiology (two patients), clostridium difficile infection (one patient), CMV colitis (one patient), concentration disturbance (one patient), benign breast lump (one patient), cervical intraepithelial neoplasia grade 1 (one patient) and non-melanoma skin cancer (one patient). Ten (7%) patients required CD-related surgery (nine bowel resection and one perianal abscess drainage).

7 | DISCUSSION

The results of our study suggest that CD patients who are nonresponsive to standard maintenance dosing of ustekinumab may benefit from dose escalation. Dose escalation was effective in about 50% of the patients, with most of the responders achieving clinical remission.

Primary and secondary nonresponse and treatment discontinuation are frequent for all treatments in IBD, including ustekinumab, with rates of treatment discontinuation approaching 40%.^{7,13} These high rates of nonresponse are not surprising considering the refractoriness of the patients included in the real-life cohorts published so far.⁹

To date, the strategy for management of loss of response to UST has not been clearly established. While for patients treated with tumour necrosis factor (TNF)-alpha inhibitors, therapeutic

drug monitoring may provide important guidance for selection of strategy.²³⁻²⁶ The correlation of ustekinumab levels with treatment outcomes is not as robust.^{6,12,27} Thus, the escalation strategy is currently empiric and nonstandardised.

Even though in the original UNITI 1/UNITI 2 trial no significant difference in the efficacy of both maintenance regimens was detected,² the endoscopic response was more frequent in the q8w maintenance arm.¹ In the long-term extension study of UNITI, patients who required dose-adjustment from q12w to q8w regimen were less likely to remain in clinical remission throughout the duration of follow-up.^{3,20} However, only a few of the recent real-world studies included a significant proportion of patients who had received the currently approved intravenous induction regimen followed by a standard q12w or q8w maintenance,^{7,13,14} as most of these studies were published before the regulatory approval of intravenous ustekinumab for Crohn's disease. The effectiveness of further dose escalation in patients who did not respond to q8w dosing has not been reported so far, with the exception of the GETAID experience reported as an abstract (57% response in 69 patients after a median of 2.1 months)²¹ and a very limited number of patients in early real-world series.^{12,16} In addition to interval shortening, a strategy of intravenous reinduction is utilised in some centres; however, the evidence to support it is minimal to date.²⁸

Our study has some limitations. Primarily, this was a multicentre retrospective study that shares common limitations with similar efforts, namely heterogeneity in treatment strategies, lack of predefined timing of visits and missing biological data. Endoscopic response was not systematically evaluated, and perianal disease reporting was subjective and not universally available. Moreover, in many patients, the escalation was attempted relatively early on, and it is possible that some of the patients could have gradually improved with standard management strategy. As mentioned, the current study was descriptive and did not allow us to compare the effectiveness of the escalation to continuation of standard maintenance dosing. Our patients were all included by university-affiliated tertiary centres; nonetheless, it is possible that additional visits to community physicians could have occurred, leading to potentially missing prescription data or dose changes. Finally, we could not

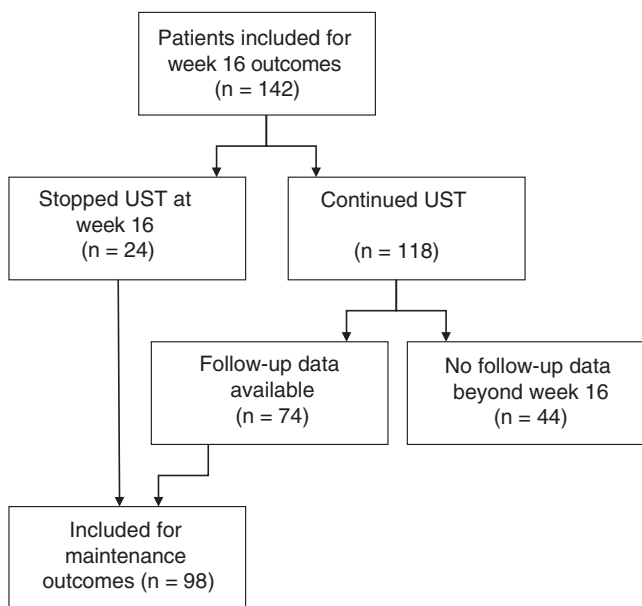


FIGURE 1 Patient inclusion chart. UST-ustekinumab

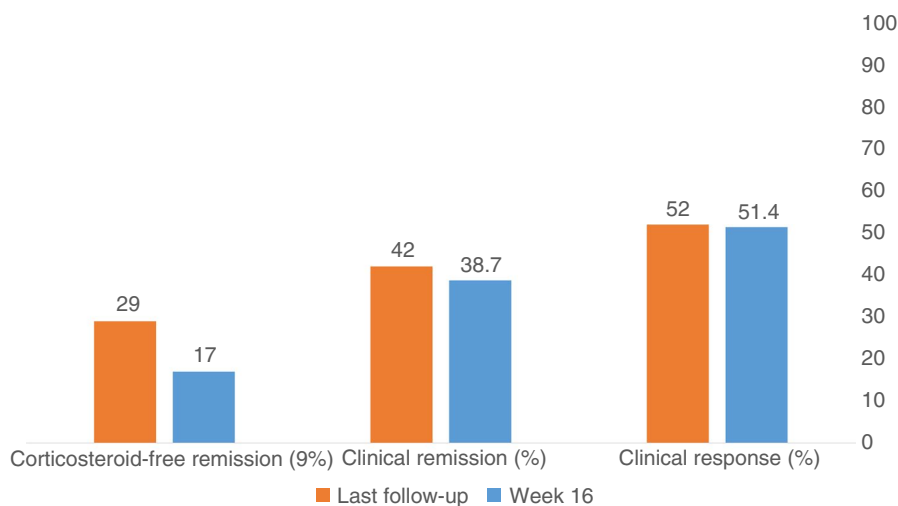


FIGURE 2 Clinical outcomes at week 16 of ustekinumab escalation and last follow-up

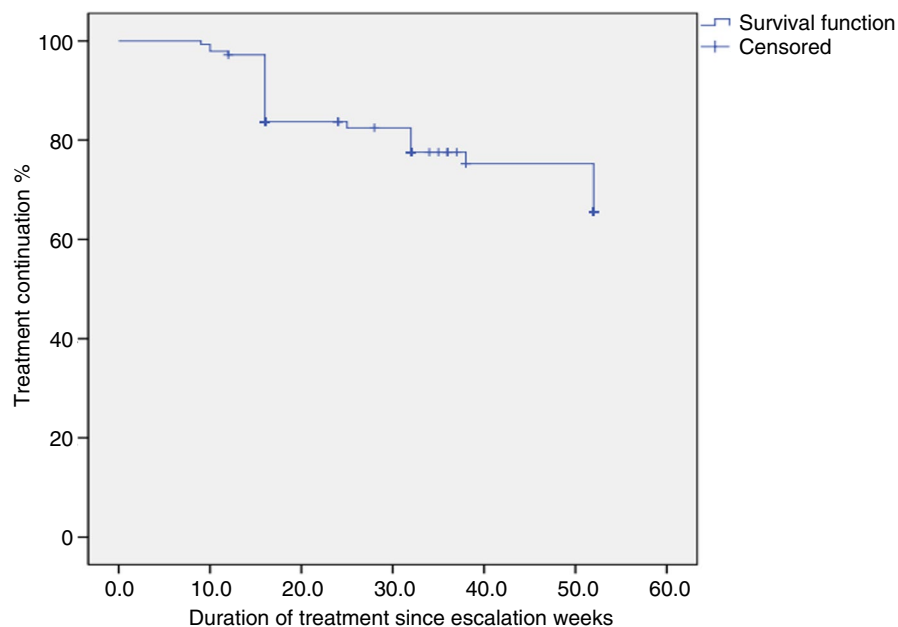


FIGURE 3 Kaplan-Meier curve of treatment discontinuation-free analysis

detect differences in efficacy between the escalation strategies, albeit the study was not powered to detect such difference.

On the other hand, this study applied stringent inclusion criteria and clear treatment outcomes (only patients with available clinical scores were included). In addition, this was a large multinational and multicentre report that maximised the amount of the available data for analysis and reflected real-life practices of IBD specialists across the ECCO community. Finally, our study did not reveal any new safety concerns; however, a retrospective study is not designed to capture mild adverse events that could have resolved without being reported to the IBD specialist.

In summary, the data accumulated in our study support the efficacy of dose escalation in CD patients who do not respond or lost response to q8w maintenance regimen. Our results merit validation in future prospective studies.

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