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Ustekinumab dose escalation improves clinical responses in refractory Crohn's disease

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Abstract

Background: Clinicians often utilize off-label dose escalation of ustekinumab (UST) in Crohn's disease (CD) patients with disease refractory to standard dosing. Previous studies report mixed results with dose escalation of UST.

Methods: A retrospective observational study of 143 adult patients with CD receiving UST over a 33-month time period was conducted. Patients receiving UST at standard dosage for a minimum of 16 weeks were included in the analysis. Primary outcomes collected were clinical response [Physician Global Assessment Score (PGA) by >1] and remission (PGA = 0). Changes in clinical parameters were calculated for dose-escalated patients beginning with the time of dose switch (~42 weeks) and compared with a group of patients who were classified as "failing" standard dosing at 42 weeks who were not dose escalated.

Results: Dose escalation improved PGA by 0.47 ± 0.19 compared with patients remaining on every 8 weeks dosing (Q8 week), who worsened by 0.23 ± 0.23 ($p < 0.05$). Dose escalation decreased CRP 0.33 ± 0.19 mg/L and increased serum albumin 0.23 ± 0.06 g/dL ($p < 0.05$). Surprisingly, disease duration and prior CD surgeries inversely correlated with the need for dose escalation.

Conclusion: Our results support UST Q4 week dose escalation for selected CD patients who fail to achieve remission on standard Q8 week dosing. Dose escalation improves clinical outcomes, prevents worsening disease severity, and positively impacts CRP and albumin levels. Together these data indicate that clinicians should attempt Q4 week UST dosing in refractory CD patients before switching to an alternative class of biologic therapy.

Keywords: Crohn's disease, dose escalation, remission, ustekinumab

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Introduction

The treatment approach to moderate to severe Crohn's disease (CD) involves biologic therapies that block TNF, α4β7 integrins on immune cells (vedolizumab) or IL-12p40/23 cytokines [ustekinumab (UST)].[1–4] UST trial data demonstrate efficacy in biologic naïve as well as anti-TNF-experienced patients.[5] UST reduces both colonic and small bowel mucosal disease, resolves fistulas, and treats extraintestinal manifestations of CD.[4,5] UST is approved in CD for a weight based intravenous (IV) induction dose followed by every 8 weeks (Q8 week) subcutaneous dosing.[2,5–7] Some clinicians report that Q8 week dose escalation to every 4 week dosing (Q4 week) improves clinical activity.[8,9]

Initial pharmaceutical clinical trials investigating UST for CD demonstrated improved responses to shorter dosing intervals in the maintenance phase (Q8 week *versus* Q12 week).[6] The UNITI-1 trial reported clinical improvement by Q6 weeks

following an induction dose in 34% of patients *versus* 20% receiving placebo.[5,6] The UNITI-2 phase II trial reported clinical improvement by Q6 weeks following induction dose of UST in 55.5% *versus* 28.7% in the placebo group.[6] These trials concluded that patients receiving maintenance Q8 week dosing were more likely to reach remission than those receiving Q12 week dosing. In the UNITI-1 study, 41.1% of patients in the Q8 week group demonstrated clinical response by 44 weeks, *versus* 38.6% of patients in the Q12 week group.[6] In the UNITI-2 study, 62.5% of patients experienced clinical remission by 44 weeks in the Q8 week group, *versus* 56.9% in the Q12 week group.[6] While the Q8 and Q12 week groups were not directly compared, this implies a benefit of increased UST dosing and supports the notion that further escalated dosing benefits some patients.

Dose escalation of anti-TNF and other biologic agents induces clinical benefit in select patients.[5,10] For patients receiving maintenance infliximab therapy, approximately 10% per year benefit from escalated dosing.[11] Increasing serum infliximab dosage was associated with normalization of CRP in inflammatory patients.[12] In a recent meta-analysis examining adalimumab dose escalation in CD, 21% of patients required dose escalation to improve responses.[13] In patients receiving dose intensification, 71% regained response and 37% achieved remission.[13] In the CHARM study, 63% of the patients who increased to adalimumab 40 mg weekly achieved remission after dose escalation.[14] Although these studies investigate the escalation of a different biologic class, they imply dose escalation could be similarly beneficial for patients receiving UST therapy. Here we aim to investigate the hypothesis that patients with moderate to severe CD who fail to achieve remission on Q8 week dosing benefit from Q4 week dose escalation.

Methods

Study design

This study was a single-institution retrospective cohort analysis of 143 adult CD patients induced and treated with UST IV loading followed by standard Q8 week dosing at an Inflammatory Bowel Disease Clinic between 1 January 2016 and 26 October 2018. Diagnosis of CD was verified by radiographic, endoscopic, and histologic criteria. Patients were excluded if they were: (a) on a non-standard dose of UST (Q12 week), (b) failed to return for follow-up after dose escalation to Q4 week, (c) had less than 16 ± 3 weeks of follow-up after the induction dose, or (d) were in remission prior to 16 ± 3 weeks.

Physician Global Assessment Disease Severity Score (PGA; 0 = remission, 1 = mild, 2 = moderate, 3 = severe) was determined retrospectively for each patient visit after reviewing chart documentation. Multiple gastroenterologists independently determined each PGA and deliberated on a consensus when a discrepancy arose. We utilized active disease after 16 weeks as the inclusion criteria decision point, as this is the timepoint reported in the literature when most patients achieved a clinical response on standard dosing.[15] To assess the impact of Q4 week dosing, we calculated the difference in clinical parameters from (a) the average time point of dose escalation (42 ± 16 weeks) compared with (b) the score at the end of follow-up. These data were compared with a group of patients who were classified as "failing" standard dosing at 42 weeks who were not dose escalated. The effect of continued Q8 week dosing was calculated as the difference from (a) clinical data at the 42 week time point compared with (b) the score at the end of follow-up. Partial response was defined as a decrease in PGA by >1. Disease remission was defined as PGA = 0. Disease non-response was defined as no change or increase in PGA score.

Patient demographic and phenotypic characteristics compared between the Q8 week control group and the Q4 week dose-escalated group included: age, gender, smoking status, duration of disease, disease location along the gastrointestinal (GI) tract, upper GI involvement, perianal disease, extent of stricture and penetration, prior anti-TNF exposure, prior thiopurine use, prior methotrexate use, prior vedolizumab usage, and prior CD related surgery. Secondary outcomes of treatment collected included: patient weight, body mass index, hemoglobin, albumin, CRP, and fecal calprotectin. Missing laboratory and clinical data were excluded from analysis.

Statistical analysis

Pearson Chi-Square and Fisher's Exact Tests as appropriate were used to analyze the association between categorical variables. Two sample *t*-tests were used to compare independent continuous variables. Paired *t*-tests were used to compare

dependent variables. Confidence intervals are means ± one standard error. The level of statistical significance used was 0.05. All analyses were performed in R version 3.6.3.[16]

Ethical considerations

The study was conducted at our university after receiving approval from our university's Institutional Review Board (IRB). All data security safeguards were strictly followed as per IRB policy. This study was deemed exempt by our IRB for ethical approval. The IRB reviewed the study and waived the necessity for informed consent as the study worked with de-identified data.

Results

Patient characteristics

To examine clinical features that correlated with the need for dose escalation, patient histories were catalogued (Table 1). Notable distinctions include the inverse relationship between disease duration and CD surgeries with dose escalation. Specifically, the mean disease duration prior to UST induction was 20.1 years in the Q8 week group and 11.4 years in the Q4 week group ($p < 0.01$). In addition, the number of patients with CD surgeries was greater in Q8 week patients (93%) compared with CD patients given Q4 week dosing (47%) ($p < 0.005$). Baseline steroid usage was significantly higher in the Q8 week group, with (47%) patients on steroid therapy at the baseline visit *versus* (13%) in the Q4 week group ($p < 0.05$).

Distribution of disease phenotypes, patient demographic characteristics, and previously attempted biologic therapies were otherwise similar between groups. All patients in the dose-escalated group had previous anti-TNF exposure compared with 93% in the Q8 week standard group ($p = 0.33$). At baseline, 67% of patients in the Q4 week group were receiving methotrexate or thiopurine, while the same was true for 80% of the Q8 week control group ($p = 0.33$). Prior vedolizumab use was similar between the Q8 week group (53%) and Q4 week group (53%) ($p = 1.00$).

At the 42-week decision point, the mean albumin of the patients in the Q8 week group was 3.6 ± 0.2 and 3.4 ± 0.3 in the Q4 week group ($p = 0.30$). The mean CRP of the patients in the Q8 week group was 0.6 ± 0.1 and 1.1 ± 0.2 in the Q4 week group ($p = 0.004$). The mean PGA of the patients in the Q8 week group was 1.4 ± 0.1 and 2.0 ± 0.2 in the Q4 week group ($p = 0.02$). Together these results suggest that disease activity for Q4 week patients was equivalent to or greater than Q8 week patients.

Dose escalation improves PGA in CD patients refractory to Q8 week dosing

Remission was achieved by 16 ± 3 weeks in 44/143 (31%) of patients receiving standard Q8 week dosing. Thirteen of 143 (9%) patients were discontinued from UST before the 16-week time point therapy due to insurance issues or adverse reactions. The remaining 86 patients (61%) remained clinically active (PGA ⩾1) at 16 ± 3 weeks. Of these 86 patients with documented disease activity at the 16-week time point, 27 went on to eventual Q4 week dose escalation. Mean time to dose escalation was 42 ± 16.4 weeks after induction. The remaining 59 patients were left on standard Q8 week UST until the end of follow-up. The decision to dose escalate was reached jointly by the patient and clinician based on the patient's prior history and management preferences. Among the 27 patients who were dose-escalated, 12 (44.4%) patients lacked a follow-up visit after escalation and were excluded, leaving $n = 15$ in the treatment dose-escalated group. To allow for direct comparison between treatment groups, we also excluded 44 "failing" patients on UST standard dosing who lacked 42 ± 16 weeks of follow-up, leaving 15 patients in the standard dosing group (Figure 1). The average length of follow-up after the baseline visit was 78 ± 28 weeks in the Q4 week dose-escalated group, and 64 ± 14 weeks in the Q8 week group. This follow-up time represents the total duration of UST therapy (Figure 1). Patients were maintained on a Q4 week treatment regimen for a mean time of 29 ± 8 weeks (decision point until end of follow-up). The mean time patients were continued on standard Q8 week dosing after the 42 ± 16-week visit was 22 ± 6 weeks (to end of follow-up).

Clinical improvement

In the Q4 week group, PGA decreased a mean value of –0.47 from the dose-escalation visit to the end of follow-up. Conversely, in the Q8 week group, the PGA increased a mean value of 0.23 from 42 weeks on standard dosing to the end of follow-up ($p < 0.02$) (Figure 2). Among the 25

Table 1. Patient demographic and phenotypic characteristics for Q4 and Q8 week treatment dose groups. Shown are baseline characteristics prior to ustekinumab induction for all patients, refractory patients maintained on Q8 week therapy for >42 weeks, and refractory patients dose-escalated to Q4 weeks. *p*-values are listed for comparisons between Q8 and Q4 weeks groups.

Baseline characteristic	All patients *n* = 143	Q8 week *n* = 15	Q4 week *n* = 15	*p*-value*
Age, years	42.2 (18–83)	49.6 (22–77)	39.4 (21–71)	0.10
Male sex, *n* (%)	63 (44.1%)	7 (46.7%)	11 (73.3%)	0.14
Current smoker, *n* (%)	35 (24.6%)	4 (26.7%)	5 (33.3%)	0.71
Duration of disease, years	14.3 (1–38)	20.1 (6–38)	11.4 (2–24)	0.008*
Prior CD related surgery, *n* (%)	94 (65.7%)	14 (93.3%)	7 (46.7%)	0.005*
Upper GI involvement, *n* (%)	33 (23.2%)	1 (6.7%)	3 (20.0%)	0.3
Disease location, *n* (%)				
Ileum	24 (16.8%)	3 (20.0%)	4 (26.7%)	0.68
Colon	37 (25.9%)	3 (20.0%)	1 (6.7%)	0.3
Ileocolonic	82 (57.3%)	9 (60.0%)	10 (66.7%)	0.71
Perianal disease, *n* (%)	34 (23.9%)	1 (6.7%)	3 (20.0%)	0.3
Disease phenotype				
Non-stricturing/non-penetrating (B1)	53 (37.1%)	5 (33.3%)	7 (46.7%)	0.47
Stricturing (B2)	55 (38.5%)	8 (53.3%)	5 (33.3%)	0.29
Penetrating (B3)	45 (31.5%)	2 (13.3%)	3 (20.0%)	0.64
Prior anti-TNF therapy, *n* (%)	131 (91.6%)	14 (93.3%)	15 (100%)	0.33
Prior vedolizumab use, *n* (%)	52 (36.4%)	8 (53.3%)	8 (53.3%)	1.00
AZA/6-MP use, *n* (%)	94 (65.7%)	12 (80.0%)	10 (66.7%)	0.43
MTX use, *n* (%)	51 (35.7%)	9 (60.0%)	7 (46.7%)	0.48
Corticosteroid use, *n* (%)		7 (46.7%)	2 (13.3%)	0.05*

AZA, azathioprine; CD, Crohn's disease; GI, gastrointestinal; MTX, methotrexate; Q4 week, every 4 weeks; Q8 week, every 8 weeks.
*Indicates a statistically significant difference between Q4 week and Q8 week groups.

patients continued on Q8 week standard dosing after failing to achieve remission at 42 ± 16 weeks, $n = 1$ patient (7%) went on to achieve remission (PGA 0) by the end of follow-up. Reduction in PGA was seen in $n = 1$ patient (7%); this patient was considered a partial responder. The remaining 86% of patients did not achieve further clinical benefit from standard dosing and remained non-responders. Among the 15 patients in the dose-escalated Q4 week group, two (13.3%) achieved remission and five (33.3%) had a further clinical response as measured by reduction in PGA. The remaining eight (53.3%) patients experienced no further change in PGA by the end of follow-up. Notably, no patients in the Q4 week group experienced a worsening of clinical disease, whereas six patients (40%) in the Q8 week group displayed worse clinical disease as measured by an increase in PGA by the end of follow-up.

Secondary outcomes

In the Q8 week group, CRP increased a mean of 0.41 mg/L from the 42-week decision point to the

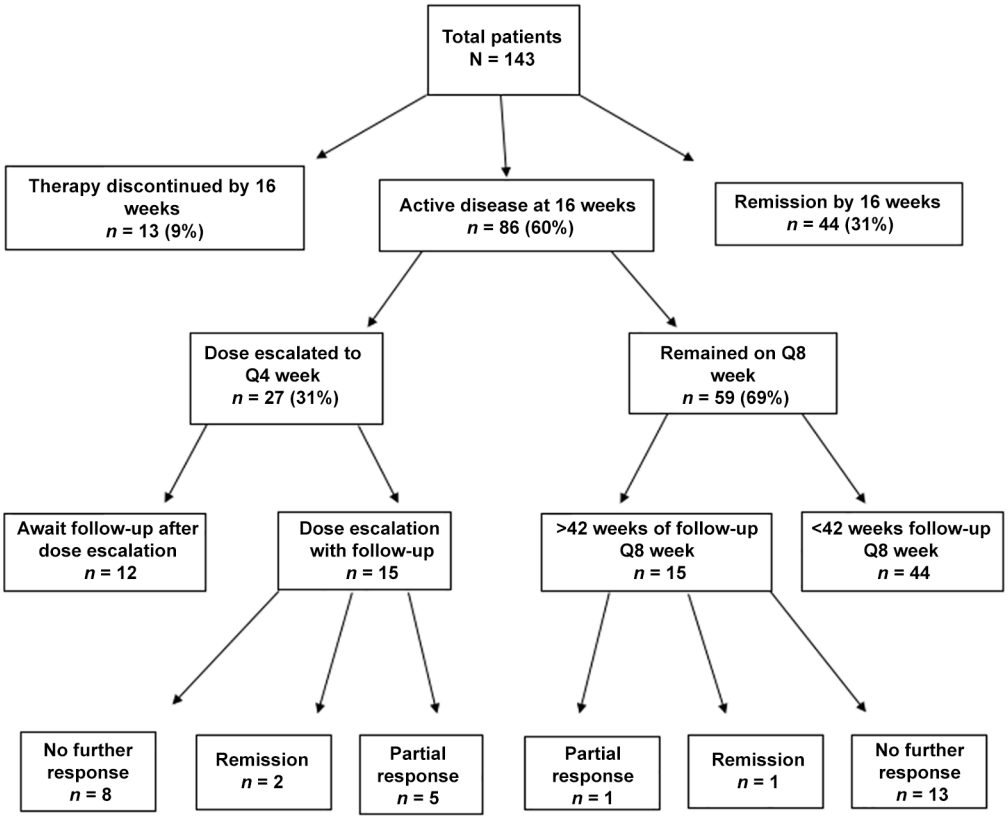

Figure 1. Breakdown of clinical responses in 143 ustekinumab (UST)-treated patients. Remission was achieved by 16 ± 3 weeks in 31% of patients receiving standard every 8 week (Q8 week) dosing. The remaining 86 patients remained active (Physician Global Assessment Disease Severity Score ⩾1) at 16 ± 3 weeks. Thirteen patients discontinued UST before the 16-week time point. Of these 86 patients with documented disease activity at the 16-week time point, 27 went on to Q4 week dose escalation. The remaining 59 patients were left on standard Q8 week dosing until the end of follow-up. Among the 27 patients who were dose-escalated, 42 ± 16 weeks was the mean time to dose escalation. Twelve patients lacked a follow-up visit and were excluded, leaving 15 in the dose-escalated group. In the standard-dose group, 44 "failing" patients lacked 42 weeks of follow-up and were excluded from analysis, leaving 15 in the standard-dose group.

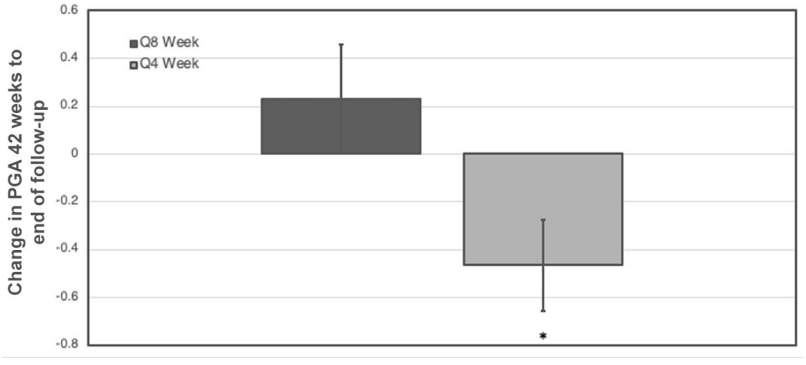

Figure 2. Dose escalation improves Physician Global Assessment Disease Severity Score (PGA) in patients who fail standard every 8 week (Q8 week) dosing. Crohn's disease patients who did not achieve remission on standard dose (Q8 week) therapy by the 42 ± 16 time point and remained on standard therapy ($n = 15$) were compared with those who were dose-escalated to Q4 week ($n = 15$). The transition to Q4 week dosing improved PGA by 0.47 ± 0.19 (dark) whereas patients who remained on Q8 week dosing exhibited a mean increase in PGA of 0.23 ± 0.23 ($p < 0.02$).

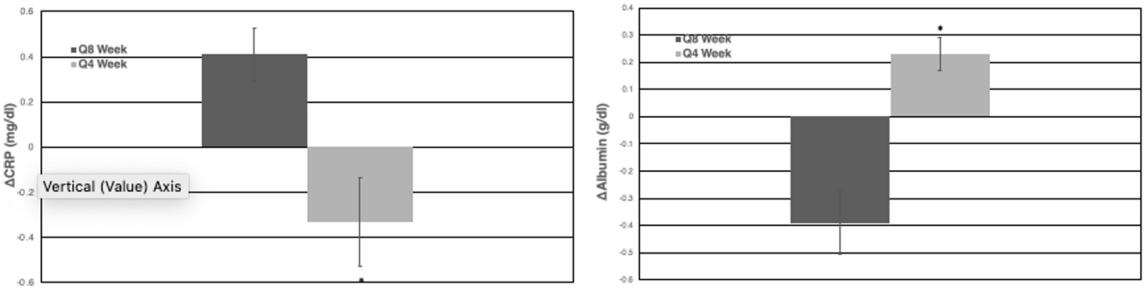

Figure 3. Dose escalation improves biomarkers of disease activity in Crohn's disease (CD) patients failing standard every 8 weeks (Q8 week) dosing. (A) Changes in CRP (ΔCRP) levels are shown for CD patients remaining on Q8 week dosing (dark) compared with those escalated to Q4 week (gray) dosing. * $p < 0.01$. (B) Changes in serum albumin (ΔAlbumin) for CD patients kept on Q8 week (dark) compared with Q4 week (gray) dosing. *$p < 0.0001$.

Table 2. Immunosuppressive agent and steroid usage between every 8 week (Q8 week) and Q4 week groups. Shown is usage at the baseline visit and at the end of follow-up for each dosing group.

Therapeutic agent	Standard Q8 week dosing baseline (*n*)	Standard Q8 week dosing at end of follow-up (*n*)	Q4 week dose-escalated group at baseline (*n*)	Q4 week dose-escalated group at end of follow-up (*n*)	*p*-value baseline	*p*-value end of follow-up
Steroid usage	7	3	2	7	0.05*	0.24
MTX or AZA usage	12	3	10	7	0.48	0.24

AZA, azathioprine; MTX, methotrexate; Q4 week, every 4 weeks; Q8 week, every 8 weeks. P-values columns compare Q8 week group and Q4 week group.
*Denotes statistical significance between the Q8 week group and the Q4 week group.

end of follow-up. Conversely, in the Q4 week group, CRP decreased a mean 0.33 mg/L from the dose-escalation visit until the end of follow-up ($p < 0.01$). In the Q8 week group, albumin decreased a mean of 0.39 g/dL from the 42-week decision point until the end of follow-up. In the Q4 week group albumin increased 0.22 g/dL from the dose escalation to the end of follow-up ($p < 0.01$) (Figure 3).

In the Q4 week dose-escalated group, seven patients (47%) remained on steroid therapy at the end of follow-up. In the Q8 week group, three patients (14%) were on steroid therapy at the end of follow-up ($p > 0.05$). However, five of these seven patients in the Q4 week group were already on steroid therapy prior to dose escalation, and these steroid doses remained unchanged to the end of follow-up. In the Q4 week dose-escalated group, seven (47%) patients were receiving MTX (methotrexate) or AZA (azathioprine) at the end of follow-up. In the Q8 week group, three (14%) were receiving MTX or AZA at the end of follow-up. ($p > 0.05$) (Table 2). Similarly, these seven Q4 week patients were receiving MTX or AZA prior to escalation, and doses were unchanged by end of follow-up.

Discussion

Treatment of severe CD has improved with the advent of several potent biologic therapies. However, in many cases persistent disease activity forces clinicians to improvise therapeutic strategies for inducing deep remission while avoiding steroids or surgery.[5] Our study examined the efficacy of UST Q4 week dose escalation among CD patients with active disease (PGA > 1). We note that patients in the Q4 week group were significantly less likely to experience a worsening of disease burden ($p < 0.05$), and patients dose escalated to Q4 weeks experienced significant improvement in PGA when compared with patients continued on standard dosing ($p < 0.05$).

This suggests dose escalation is especially valuable for patients who are susceptible to frequent disease flares.

We note that patients in the Q4 week dose-escalated group experienced greater improvements in secondary outcomes such as albumin and CRP *versus* patients that remained on standard Q8 week dosing (Figure 3). Dose-escalated patients showed an impressive absolute decrease in CRP compared with patients left on standard dosing ($p < 0.01$) (Figure 3). In CD, CRP strongly correlates with disease activity and is closely associated with Crohn's Disease Activity Index (CDAI).[17] Albumin also significantly increased in the Q4 week group and decreased in the Q8 week group ($p < 0.0001$). These findings support the decision to dose escalate UST in CD patients doing poorly on Q8 week dosing.

It is important to point out that our cohort consisted almost entirely of treatment-resistant CD patients. Nearly all the patients failed more than one anti-TNF biologic therapy, and many failed multiple biologic agents (Table 1). This potentially explains why only 31% of our cohort ($n = 44$) achieved remission by week 16 ± 3 on standard Q8 week dose, a significantly lower percentage than reported elsewhere.[15] This suggests our cohort of patients may be inherently treatment resistant and more likely to require dose escalation. This is further supported by a long mean disease duration prior to UST induction for both the Q8 week group (20.1 years) and the Q4 week group (11.4 years) ($p < 0.01$). UST is often added to a therapeutic regimen after a patient has failed initial immunomodulator therapy or previous biologic agents.[5] The shorter time interval to UST induction in our Q4 week group suggests a more severe disease phenotype as it took less time to escalate the therapeutic treatment regimen. The discrepancy in disease duration prior to UST induction could also explain the significant difference in CD related surgery. There was a significant difference in surgical experience between groups, 93% of patients in the control group had documented prior CD related surgery as compared with 46.6% of patients in the Q4 week group ($p < 0.01$) (Table 1). The introduction of biologics for treatment for CD has increased the threshold for surgical treatment. The average disease duration in the Q8 week group pre-dates the introduction of many biologic medications (adalimumab was approved for CD treatment in 2007).[18] Therefore, it is possible that surgical intervention occurred before biologic agents became available.

There are only a small number of previously reported studies regarding UST dose escalation, and the results are varied. A cohort study from McGill University reported that after Q4 week dose escalation, 11/18 (61.1%) patients demonstrated clinical improvement.[9] All the patients in this cohort were anti-TNF failures, which allows for adequate comparison with our own cohort. Another Canadian study found that only 3/16 patients dose-escalated to Q4 week exhibited clinical improvement.[19] In each of these studies, there was no standardized metric mentioned (PGA or CDAI) to gauge clinical improvement. A recently conducted study from the University of Chicago reported that dose escalation to Q4 week resulted in significant improvement in CRP, and 28% of patients with active disease went on to achieve clinical remission.[8] Clinical improvement was defined by a reduction in the Harvey Bradshaw Index.[8] These results are consistent with our study's findings. Together these results support the recommendation that UST dose escalation should be considered prior to switching therapeutic classes.

A significantly larger number of patients in the Q4 week patients were receiving steroid, AZA, or MTX therapies compared with the Q8 week group by the end of follow-up: 47% *versus* 14% ($p > 0.05$) (Table 2). However, 5/7 of the patients in the Q4 week group that were on steroids were taking MTX or AZA therapy before dose escalation. Furthermore, the dosages of steroids and immunomodulators were the same before the dose escalation intervention and at the end of follow-up. The lack of disease progression cannot be conclusively attributed to steroid or immunomodulatory therapy, as most patients receiving these therapies at the end of follow-up were receiving them before the intervention occurred.

A significant limitation of this study is the retrospective design. Patients were not randomized, and the decision point to dose escalate to Q4 week was multifactorial, based on subjective clinical factors, financial variables, and a joint decision between provider and patient. There were no objective criteria for which patients were selected to be dose-escalated, other than PGA > 1 after 16 ± 3 weeks of standard dosing. The subjective inclusion criteria of the dose-escalated group potentiates selection bias. However, at the

42-week decision point, patients in the Q4 week group had a higher mean PGA than in the Q8 week group (2.0 ± 0.2 and 1.4 ± 0.1 respectively). Despite having a worse disease phenotype at the point of escalation, patients in the Q4 week group still experienced a significant reduction in disease burden relative to the Q8 week group. We also note that while PGA has been used as a gold-standard assessment, it is limited by its dependence on subjective physician assessment. We did not have consistent objective data, such as endoscopic assessment or fecal calprotectin, to use instead of clinical assessment. This study was also limited by an inadequate duration of follow-up by the time of study conclusion, resulting in the exclusion of nearly half (12/27) of the patients who received escalated UST dosing. Over half of the patients in the Q8 week dosing group (44/59) were also excluded for inadequate follow-up duration (Figure 1). This degree of necessary exclusion, unfortunately, impacts the power of our analysis. Finally, we were unable to analyze blood levels of UST due to a lack of clinically available assays at the time of the study. However, this is likely of less importance given that there is currently limited consensus for optimal UST trough levels.[20] Further studies are needed to determine whether measuring UST blood levels circumvents variation in drug clearance between patients and allows for easier dose-escalation decisions.

Conclusion

Our results indicate dose escalation to Q4 week should be considered for CD patients who do not achieve remission by 16 weeks on standard Q8 week dosing. Given the relative safety of this drug and efficacy in anti-TNF-experienced patients, we propose that clinicians resist changing to alternative biologic therapies until a trial of Q4 week dosing is attempted.

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Conflict of interest statement

TAB has consulted and received honoraria for speaker's bureau activities for Takeda and AbbVie pharmaceutical companies. None of the other authors have any conflict of interest to disclose.

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