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INFLAMMATORY BOWEL DISEASE

Real-World Experience With Tofacitinib Dose De-Escalation in Patients With Moderate and Severe Ulcerative Colitis

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BACKGROUND & AIMS: **Tofacitinib is associated with sustained steroid-free remission in patients with ulcerative colitis (UC), with the lowest effective dose recommended for maintenance therapy. However, there are limited real-world data to guide decisions on the optimal maintenance regimen. We aimed to evaluate predictors and outcomes of disease activity after tofacitinib dose de-escalation in this population.**

METHODS: **Included were adults with moderate–severe UC treated with tofacitinib between June 2012 and January 2022. The primary outcome was evidence of UC disease activity–related events: hospitalization/surgery, corticosteroid initiation, tofacitinib dose increase, or therapy switch.**

RESULTS: **Among 162 patients, 52% continued 10 mg twice daily while 48% underwent dose de-escalation to 5 mg twice daily. Cumulative incidence rates of UC events at 12 months were similar in patients with and without dose de-escalation (56% vs 58%; $P = .81$). In univariable Cox regression among patients with dose de-escalation, an induction course with 10 mg twice daily for more than 16 weeks was protective of UC events (hazard ratio [HR], 0.37; 95% CI, 0.16–0.85) while ongoing severe disease (Mayo 3) was associated with UC events (HR, 6.41; 95% 95% CI, 2.23–18.44), which remained significant after adjusting for age, sex, duration of induction course, and corticosteroid use at dose de-escalation (HR, 6.05; 95% CI, 2.00–18.35). Twenty-nine percent of patients with UC events had their dose re-escalated to 10 mg twice daily, with only 63% able to recapture clinical response at 12 months.**

CONCLUSIONS: **In this real-world cohort, we observed a 56% cumulative incidence of UC events at 12 months in patients with tofacitinib dose de-escalation. Observed factors associated with UC events after dose de-escalation included induction course for fewer than 16 weeks and active endoscopic disease 6 months after initiation.**

Keywords: Outcomes; Flare; Janus Kinase Inhibitor; Inflammatory Bowel Disease.

Tofacitinib is the first oral, small-molecule pan–Janus kinase inhibitor approved for the treatment of moderate to severe ulcerative colitis (UC) with demonstrated efficacy and safety as induction and maintenance therapy.[1,2] Currently, tofacitinib is approved at a dose of 10 mg twice daily for up to 16 weeks for induction, and at a dose of 5 mg twice daily for maintenance—or the lowest effective dose needed to maintain response.[1,3] Dose de-escalation generally is encouraged based on a reduced risk of dose-dependent side effects related to increased venous thromboembolic events observed in rheumatoid arthritis patients treated with tofacitinib 10 mg twice daily.[3–5]

However, dose de-escalation may not be appropriate for every patient. In clinical practice, many patients with UC may require an extended induction period or re-induction after dose de-escalation to recapture clinical response. The OCTAVE trial showed consistent safety and efficacy at both the 5-mg and 10-mg dosage for up to 36 months; however, a small subgroup of patients de-escalated to 5 mg twice daily (19%), leading to one fourth of patients experiencing loss of response by 12

Abbreviations used in this paper: HR, hazard ratio; VTE, venous thromboembolism; UC, ulcerative colitis.

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months with only one-half able to recapture clinical response after re-induction.[6,7] In the RIVETING trial, one fifth of patients in stable remission on 10 mg twice daily experienced a UC flare after dose de-escalation and not all were able to recapture clinical response despite re-induction to 10 mg twice daily.[8]

Although prior real-world studies have reported consistent efficacy rates with tofacitinib in achieving steroid-free remission, there are limited real-world data on clinical outcomes after dose de-escalation per drug label to guide decisions on optimal maintenance regimens—specifically, which individuals may benefit with continuation of induction dose.[9–12] Importantly, patients may experience a disease flare and/or loss of response after de-escalation without the ability to recapture clinical response. Therefore, we aimed to describe clinical outcomes after tofacitinib dose de-escalation after induction and to identify predictors of UC disease activity–related events after dose de-escalation in UC patients in a real-world setting.

What You Need to Know

Background

Tofacitinib is approved for treatment of moderate to severe ulcerative colitis with recommended dose de-escalation after 8 to 16 weeks. Limited real-world data are available for outcomes after dose de-escalation.

Findings

More than half of patients with tofacitinib dose de-escalation experienced worse disease activity, which was associated with an induction course for fewer than 16 weeks and active endoscopic disease activity at 6 months after initiation.

Implications for patient care

Providers should balance risks and benefits of extending tofacitinib 10 mg twice daily dosing for more than 16 weeks for ulcerative colitis patients, especially in those with active endoscopic disease before dose de-escalation.

Materials and Methods

Study Population

We conducted a retrospective cohort study of adults aged 18 years or older with a diagnosis of UC who were evaluated in the ambulatory setting at a single academic medical center between June 2012 and January 2022 and had current and/or prior therapy with tofacitinib. Patients initially were identified using International Classification of Diseases, 9th and 10th revisions, clinical modification codes for UC (International Classification of Diseases, 9th revision, Clinical Modification code 556.x, and International Classification of Diseases, 10th revision, Clinical Modification code K51.xx), followed by manual chart review by trained study personnel to confirm the UC diagnosis and to identify patients prescribed tofacitinib to be included in the cohort. The baseline date were defined as the tofacitinib start date. Patients were excluded if they had concurrent use of biologic therapy at the time of tofacitinib initiation, prior colectomy with resection of 50% or more of the colon, or a diagnosis of Crohn's disease or indeterminate colitis.

This study was approved by the Institutional Review Board at the University of California, San Francisco (San Francisco, CA).

Definition of Covariates and Treatment Outcomes

Demographic and clinical data including sex, race/ethnicity, age at UC diagnosis, age at tofacitinib initiation, and duration of disease at time of tofacitinib initiation were abstracted manually from the electronic health record. Disease extent classifications included proctitis, left-sided, or extensive (ie, pancolitis). Prior and current use of medical therapies including aminosalicylates (including mesalamine, sulfasalazine, balsalazide), systemic corticosteroids (oral or intravenous), topical therapies (steroid/mesalamine enemas or suppositories), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and biologics (infliximab, adalimumab, certolizumab, golimumab, natalizumab, vedolizumab, and ustekinumab) were recorded in the 2 months preceding and during tofacitinib induction. We additionally noted the duration of the induction course with tofacitinib 10 mg twice daily, categorized as induction periods of 8 weeks, 16 weeks, or longer than 16 weeks, and whether dose de-escalation occurred within 12 months after initiation and/or if patients required hospitalization at the time of tofacitinib induction. We assessed baseline disease severity based on the endoscopic Mayo score at 6 months before tofacitinib initiation (noting the most severe segment on colonoscopy or flexible sigmoidoscopy report), as well as the presence of rectal bleeding and patient-reported average daily stool frequency as documented in the clinical notes. To be all inclusive of different intervals of dose de-escalation, as well as to include clinical and/or endoscopic assessments in patients who did not de-escalate or de-escalated after 6 months, we evaluated all available clinical and/or endoscopic assessments at 6 months after tofacitinib initiation for consistency. In patients who de-escalated, overall disease severity was assessed at the time of dose de-escalation (if de-escalated before 6 months) or at 6 months after tofacitinib initiation (if de-escalated after 6 months) using clinical response per physician assessment based on gastroenterology provider notes and/or complete endoscopic remission (defined as a Mayo score of 0 in the entire examined colon). In patients

who did not de-escalate, clinical and/or endoscopic response was assessed at 6 months after therapy initiation. In addition, we recorded new diagnoses of venous thromboembolism (VTE) or major adverse cardiovascular events during the duration of tofacitinib therapy.

Our primary study outcome was UC disease activity–related events (UC events) in the 12 months after tofacitinib initiation regardless of whether de-escalation occurred, defined as at least 1 of the following: (1) UC-related hospitalization in which UC was determined to be the primary diagnosis at discharge; (2) UC-related surgery; (3) new initiation of oral or intravenous corticosteroids; (4) change to another UC therapy (including the addition of a biologic for dual therapy); or (5) re-escalation to tofacitinib 10 mg twice daily after dose de-escalation. Moreover, these events were evaluated based on the earlier-described criteria regardless of whether the patient de-escalated to 5 mg twice daily or had corticosteroid use preceding or during tofacitinib induction. For patients who required dose re-escalation to 10 mg twice daily, recapture of clinical response was based on clinical and/or endoscopic findings.

Statistical Analysis

Data were presented as numbers and percentages for categoric variables or as means and SDs vs medians and interquartile ranges for continuous variables. Variables were compared by using the *t* test and Pearson chi-square test, as appropriate. The time to the UC disease activity–related event was defined as the time from tofacitinib dose de-escalation to the UC event and was censored at the last known date of clinical follow-up evaluation. The cumulative incidence rate of the UC event after dose de-escalation was summarized using the Kaplan–Meier method and compared between groups using the log-rank test. Time-to-event analyses with Cox regression were used to determine the association between tofacitinib dose de-escalation and UC disease activity–related event(s); established clinical prognostic factors of UC event(s) and candidate predictors with a *P* value less than .10 in the univariable analysis were evaluated for inclusion in the final multivariable model. A 2-sided *P* value less than .05 was considered statistically significant. Analyses were performed using STATA, version 15.1 (StataCorp, College Station, TX).

Results

Baseline Patient Characteristics

We identified 162 patients with a diagnosis of UC who were treated with tofacitinib during our study period from June 2012 to January 2022. Among these patients, 87 (54%) were male and 115 (71%) were of White race/ethnicity with a median age of 35 years (interquartile range, 28–46 y) at the time of tofacitinib initiation. Baseline characteristics of patients who maintained the induction dose vs de-escalation dose are shown in Table 1. Eighty-four (52%) patients continued the induction dose at 10 mg twice daily while 78 (48%) de-escalated to 5 mg twice daily. Among the 78 patients who de-escalated, 23 (or 29%) patients had dose de-escalation occurring more than 16 weeks after tofacitinib initiation after a median initiation duration of 8 months (interquartile range, 6–10 mo). Both groups had similar demographic characteristics including age, ethnicity, and body mass index, as well as baseline disease factors including age at diagnosis, duration of disease, age at tofacitinib initiation, and extent of disease. Compared with patients who maintained the induction dose, patients with dose de-escalation were less likely to have received oral or intravenous corticosteroids in the 2 months preceding tofacitinib induction (46% vs 67%; $P = .01$) or during induction (50% vs 70%; $P = .01$). There was no difference in other medication use before or during induction, number of prior biologics used, endoscopic Mayo score before induction, or clinical factors within 6 months before tofacitinib induction including stool frequency or presence of rectal bleeding between both groups.

Treatment Outcome Among Dose Continuation and De-Escalation

Characteristics and treatment outcomes at the 6-month follow-up evaluation among those who de-escalated tofacitinib therapy to 5 mg twice daily vs those who continued 10 mg twice daily are shown in Table 2. At the 6-month follow-up evaluation, patients who continued tofacitinib at 10 mg twice daily reported higher mean daily stool frequency (5.1 vs 3.8 stools/d) and more rectal bleeding (44% vs 30%) compared with those who de-escalated to 5 mg twice daily. Those who de-escalated were more likely to have demonstrated clinical response based on physician assessment (69% vs 42%; $P < .01$), but did not have a statistically significant difference in proportion with complete endoscopic remission (22% vs 14%; $P = .21$). A total of 92 patients (57%) experienced a UC event within 12 months after tofacitinib initiation. The cumulative event rate between those who de-escalated to 5 mg twice daily vs those who continued 10 mg twice daily was similar (56% vs 58%; $P = .81$). Patients who continued 10 mg twice daily had higher proportions of a UC-related hospitalization (27% vs 14%; $P = .04$) and therapy switch (39% vs 13%; $P < .01$) compared with those who de-escalated. Twenty-seven patients (17%) who de-escalated therapy required re-escalation to 10 mg twice daily. Among those who re-escalated to 10 mg twice daily, the majority (17 of 27 patients; 63%) were able to recapture clinical response at the higher dosage of 10 mg twice daily. Of the patients with dose re-escalation who had an available

Table 1. Baseline Characteristics of Ulcerative Colitis Patients Stratified by Tofacitinib De-Escalation

	Total, n = 162	De-escalation, n = 78	Continuation, n = 84	*P* value
Sex, male	87 (54)	43 (55)	44 (52)	.73
Race				.11
White	115 (71)	59 (77)	56 (67)	
Black	2 (1)	1 (1)	1 (1)	
Hispanic	8 (5)	2 (3)	6 (7)	
Asian	21 (13)	12 (16)	9 (11)	
Other	15 (9)	3 (4)	12 (14)	
Body mass index, kg/m^2	24.8 ± 5.5	24.3 ± 4.7	25.3 ± 6.1	.26
Age at diagnosis, *y*	27 (19–35)	28 (20–35)	26 (18–35)	.25
Age at tofacitinib initiation, *y*	35 (28–46)	37 (29–45)	35 (27–46)	.54
Disease duration, *y*	6 (3–13)	6 (3–11)	6 (2–16)	.16
Disease distribution				.21
Proctitis	6 (4)	5 (6)	1 (1)	
Left-sided colitis	50 (31)	23 (30)	27 (32)	
Pancolitis	106 (65)	50 (64)	56 (67)	
Prior biologic failure	155 (96)	73 (94)	82 (98)	.21
Prior biologic failures, n	2.0 ± 1.0	2.0 ± 1.0	2.0 ± 0.9	.99
Hospitalized at time of tofacitinib induction	30 (19)	13 (17)	17 (20)	.56
Therapy in preceding 2 months before tofacitinib				
Corticosteroids	92 (57)	36 (46)	56 (67)	.01
Oral aminosalicylates	18 (11)	11 (14)	7 (8)	.24
Topical therapy	25 (15)	15 (19)	10 (12)	.20
Immunomodulators	32 (20)	16 (21)	16 (19)	.81
Biologics	144 (89)	67 (86)	77 (92)	.24
Stools reported at time of induction, n	8.3 ± 4.2	7.8 ± 3.9	8.7 ± 4.4	.18
Rectal bleeding at induction	111 (72)	51 (70)	60 (73)	.65
Induction Mayo score				.73
0	2 (1)	1 (1)	1 (1)	
1	10 (7)	6 (8)	4 (5)	
2	63 (41)	33 (44)	30 (39)	
3	78 (51)	35 (7)	43 (55)	
Therapy during tofacitinib induction				
Corticosteroids	98 (61)	39 (50)	59 (70)	.01
Oral aminosalicylates	12 (7)	8 (10)	4 (5)	.18
Topical therapy	23 (14)	12 (15)	11 (13)	.68
Immunomodulators	4 (3)	3 (4)	1 (1)	.35

NOTE. Values are reported as number (percentage), means ± SD, or median (interquartile range).

endoscopic evaluation (n = 5) at 12 months, all achieved endoscopic response with Mayo 0 or 1 disease. Among the 10 patients (37%) who were not able to recapture clinical response after dose re-escalation, 4 patients (40%) required UC-related surgery, 6 patients (60%) required a change in therapy, and 5 patients (50%) required hospitalization. In our overall cohort, 2 patients were found to have deep venous thrombosis: 1 patient at 8 months after tofacitinib initiation at 5 mg twice daily dosing, and the second patient at 9 months after tofacitinib initiation at 10 mg twice daily dosing in the setting of a peripherally inserted central catheter line placement (Supplementary Table 1). There were no deaths observed during the entire study follow-up duration.

Clinical Factors Associated With Ulcerative Colitis Disease Activity–Related Events After Dose De-Escalation

Baseline demographic and clinical characteristics of all patients regardless of dose de-escalation who had 1 or more UC disease activity–related events are shown in Supplementary Table 2. Compared with patients who maintained remission, patients with UC event(s) had significantly higher rates of corticosteroid use during induction (69% vs 49%; $P = .01$), but were similar in other clinical aspects including disease distribution, duration of induction course, other therapy use preceding or during induction, and endoscopic Mayo disease score. At the 6-month follow-up evaluation, patients with

Table 2. Six-Month Follow-Up Characteristics and 12-Month Outcomes After Tofacitinib Treatment Initiation Stratified by Tofacitinib De-Escalation Vs Continuation

	Total, n = 162	De-escalation, n = 78	Continuation, n = 84	*P* value
Stools reported at 6 months, n	4.5 ± 3.4	3.8 ± 2.8	5.1 ± 3.8	.01
Rectal bleeding at 6 months	58 (38)	22 (30)	36 (44)	.07
Mayo score at 6 months				.45
0	29 (24)	16 (27)	13 (21)	
1	28 (23)	16 (27)	12 (19)	
2	31 (25)	13 (22)	18 (29)	
3	34 (28)	14 (24)	20 (32)	
Physician assessment of clinical response	87 (55)	53 (69)	34 (42)	<.01
Complete endoscopic remission	26 (18)	15 (22)	11 (14)	.21
UC disease activity–related event	92 (57)	44 (56)	49 (58)	.81
UC-related surgery	34 (21)	12 (15)	22 (26)	.09
UC-related hospitalization	34 (21)	11 (14)	23 (27)	.04
Initiation of oral/intravenous corticosteroids	33 (20)	14 (18)	19 (23)	.46
Change in therapy	43 (27)	10 (13)	33 (39)	<.01
Re-escalation to 10 mg twice daily	–	27 (17)	–	–

NOTE. Values are reported as number (percentage) or means ± SD.
UC, ulcerative colitis.

a UC event had a significantly higher mean daily stool frequency (5.7 vs 2.6), higher endoscopic Mayo scores (Mayo 3, 45% vs 6%), and lower rates of clinical response based on physician assessment (31% vs 88%). Among patients who underwent dose de-escalation, those with UC disease activity–related events were more likely to require corticosteroid therapy during induction (59% vs 38%; $P = .07$), have a shorter duration of induction, more severe endoscopic disease at the 6-month follow-up evaluation (Mayo 3, 39% vs 4%), lower rates of clinical response based on physician assessment (48% vs 97%), and lower rates of deep endoscopic remission (13% vs 37%) compared with those who maintained remission (Table 3). Among patients with dose de-escalation, cumulative rates of UC disease activity–related events at 12 months were higher in patients with active endoscopic disease (Mayo 3) after 6 months of induction (39% vs 24% had Mayo 2 vs 21% with Mayo 1 vs 15% with Mayo 0) and with a shorter induction course (46% at 8 weeks vs 34% at 16 weeks vs 21% at more than 16 weeks) (Figure 1).

Predictors of UC disease activity–related events after dose de-escalation are shown in Table 4. In univariable Cox regression, prolonged duration of tofacitinib induction course with 10 mg twice daily for more than 16 weeks was protective of UC events (hazard ratio [HR], 0.37; 95% CI, 0.16–0.85) whereas ongoing severe disease (Mayo 3) was associated with a UC event (HR, 6.41; 95% CI, 2.23–18.44), which remained significant after adjusting for age, sex, duration of induction course, and concomitant corticosteroid use at the time of dose de-escalation (HR, 6.05; 95% CI, 2.00–18.35). We then applied this model only to patients with clinical improvement (defined as non–steroid-dependent and endoscopic Mayo score of less than 3 at the 6-month follow-up evaluation after induction) who underwent dose de-escalation, of which the duration of the induction course was no longer associated with UC disease activity–related events (Supplementary Table 3).

Clinical Factors Associated With Ulcerative Colitis Disease Activity–Related Events After Induction Dose Continuation

After 12 months of follow-up evaluation, 42% of the 84 patients who continued the induction dose remained in remission while 58% experienced a UC event, with 33 (40%) requiring a change in medication after a median of 5 months (interquartile range, 4–7 mo). In univariate regression, endoscopic evidence of Mayo 3 disease at 6 months after tofacitinib initiation was associated significantly with a UC event (odds ratio, 9.58; 95% CI, 2.05–44.73). On multivariate regression after adjusting for age at tofacitinib initiation, sex, and endoscopic disease activity at the 6-month follow-up evaluation, use of corticosteroids at the time of induction was associated with a UC event (odds ratio, 3.83; 95% CI, 1.16–13.16).

Discussion

Tofacitinib remains an effective therapy for the management of ulcerative colitis and is associated with

Table 3. Baseline and 6-Month Follow-Up Characteristics in Patients With Ulcerative Colitis Disease Activity–Related Event(s) Vs Those Without, After Tofacitinib Dose De-Escalation

	Total, n = 78	Disease activity–related event, n = 44	No event, n = 34	*P* value
Sex, male	43 (55)	23 (52)	20 (59)	.56
Race				.22
White	59 (77)	32 (74)	27 (79)	
Black	1 (1)	1 (2)	0 (0)	
Hispanic	2 (3)	2 (5)	0 (0)	
Asian	12 (16)	5 (12)	7 (21)	
Other	3 (4)	3 (7)	0 (0)	
Body mass index, kg/m^2	24.3 ± 4.7	24.4 ± 4.7	24.2 ± 4.7	.84
Age at diagnosis, *y*	28 (20–35)	27 (19–38)	28 (24–32)	.47
Age at tofacitinib initiation, *y*	37 (29–45)	38 (29–46)	35 (30–45)	.74
Disease duration, *y*	6 (3–11)	6 (3–11)	7 (4–10)	.97
Disease distribution				.14
Proctitis	5 (6)	3 (7)	2 (6)	
Left-sided colitis	23 (30)	9 (21)	14 (41)	
Pancolitis	50 (64)	32 (73)	18 (53)	
Prior biologic failure	73 (94)	42 (96)	31 (91)	.44
Prior failed biologics, n	2.0 ± 1.0	2.0 ± 1.0	2.1 ± 1.2	.71
Hospitalized at time of tofacitinib induction	13 (17)	9 (21)	4 (12)	0.31
Therapy in preceding 2 months before tofacitinib				
Corticosteroids	36 (46)	23 (52)	13 (38)	.22
Oral aminosalicylates	11 (14)	7 (16)	4 (12)	.60
Topical therapy	15 (19)	7 (16)	8 (24)	.40
Immunomodulators	16 (21)	11 (25)	5 (15)	.26
Biologics	67 (86)	39 (89)	28 (82)	.43
Stools reported at time of induction, n	7.8 ± 3.9	8.2 ± 4.1	7.3 ± 3.7	.39
Rectal bleeding at induction	51 (70)	32 (78)	19 (59)	.08
Induction Mayo score				.35
0	1 (1)	0 (0)	1 (3)	
1	6 (8)	2 (5)	4 (13)	
2	33 (44)	20 (46)	13 (42)	
3	35 (47)	22 (50)	13 (42)	
Duration of induction course, *wk*				.07
8	28 (36)	20 (46)	8 (24)	
16	27 (35)	15 (34)	12 (35)	
>16	23 (29)	9 (21)	14 (41)	
Therapy during tofacitinib induction				
Corticosteroids	39 (50)	26 (59)	13 (38)	.07
Oral aminosalicylates	8 (10)	5 (11)	3 (9)	.72
Topical therapy	12 (15)	7 (16)	5 (15)	.89
Immunomodulators	3 (4)	2 (5)	1 (3)	.71
Stools reported at 6 months, n	3.8 ± 2.8	4.7 ± 3.2	2.5 ± 1.3	<.01
Rectal bleeding at 6 months	22 (30)	20 (48)	2 (7)	<.01
Mayo score at 6 months				.01
0	16 (27)	5 (15)	11 (42)	
1	16 (27)	7 (21)	9 (35)	
2	13 (22)	8 (24)	5 (19)	
3	14 (24)	13 (39)	1 (4)	
Physician assessment of clinical response	53 (69)	21 (48)	32 (97)	<.01
Complete endoscopic remission	15 (78)	5 (13)	10 (37)	.02

NOTE. Values are reported as number (percentage), means ± SD, or median (interquartile range).

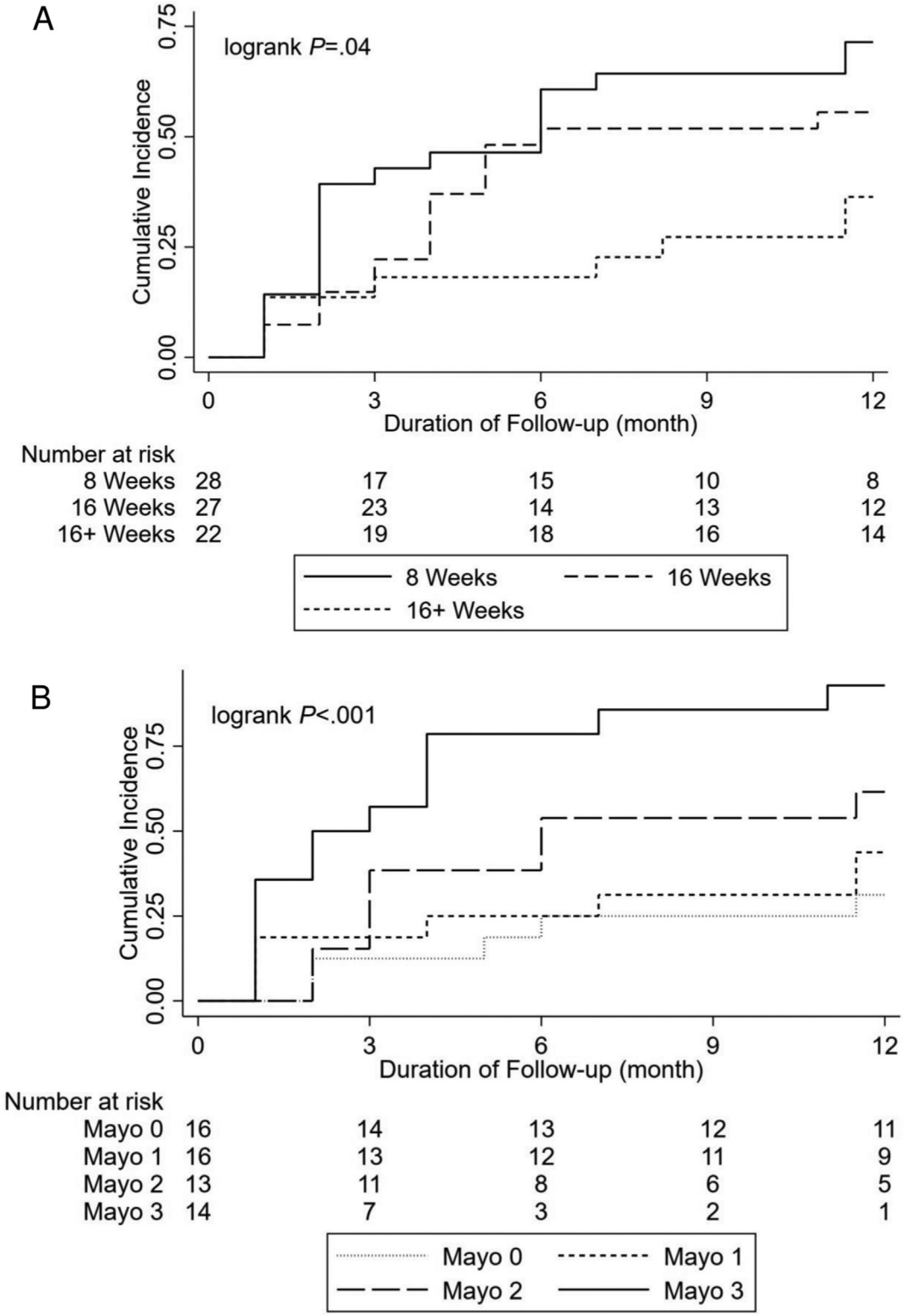

Figure 1. Cumulative incidence of ulcerative colitis disease activity–related events in patients after tofacitinib dose de-escalation, stratified by the (*A*) duration of the induction course and (*B*) Mayo endoscopic score at the 6-month follow-up evaluation after induction.

sustained steroid-free remission. Although the product label recommends dose de-escalation after 8 or 16 weeks, clinical practice is variable in the real-world setting.[13] Available data on clinical outcomes after dose de-escalation have been derived largely from registrational clinical trials, in which treatment duration and timing of dose de-escalation is based on trial design, and is not focused on patients in remission for a minimum therapy duration. In this retrospective real-world study of moderate to severe UC patients with almost

Table 4. Univariable and Multivariable Cox Regression of Predictors of Ulcerative Colitis Disease Activity–Related Event(s) in the Setting of Tofacitinib Dose De-Escalation

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex, male	1.15	0.63–2.10	.65	1.14	0.56–2.34	.72
Age at tofacitinib initiation, *y*	1.00	0.98–1.03	.85	1.01	0.98–1.05	.34
Duration of induction course, *wk*						
8	Ref	–	–	Ref	–	–
16	0.68	0.35–1.33	.26	0.63	0.28–1.40	.26
>16	0.37	0.16–0.85	.02	0.45	0.17–1.26	.13
Corticosteroid therapy during tofacitinib induction	1.76	0.96–3.24	.07	1.27	0.61–2.62	.52
Mayo score at 6 months						
0	Ref	–	–	Ref	–	–
1	1.52	0.48–4.79	.48	1.78	0.55–5.77	.34
2	2.45	0.80–7.52	.12	2.36	0.76–7.33	.14
3	6.41	2.23–18.44	<.01	6.05	2.00–18.35	<.01

HR, hazard ratio.
NOTE. Variables in the multivariable analysis included age at tofacitinib initiation, sex, duration of induction course, corticosteroid therapy during tofacitinib induction, and Mayo score at 6 months after tofacitinib initiation.

half undergoing dose de-escalation, we observed that more than half of patients experienced a UC disease activity–related event within 12 months after dose de-escalation, particularly in patients with an induction course of fewer than 16 weeks and active endoscopic disease at 6 months after induction. More importantly, in patients who underwent dose re-escalation, only 63% were able to recapture clinical response.

An important finding from our study was that more than half of the patients who underwent dose de-escalation experienced a UC disease activity–related event after a median duration of 12 weeks after dose reduction. Although dose de-escalation is preferrable for long-term maintenance therapy to reduce the potential lifetime risk of medication-related adverse events, it must be balanced with sustained remission to prevent short- and long-term disease-related complications. Our rates of relapse are higher than in previously reported studies, although with notable differences in induction periods and remission status at the time of dose de-escalation. Importantly, remission was not required or ubiquitous before dose de-escalation for some of the patients in our real-world cohort because providers' practice patterns are subjected to influence by product labeling rather than clinical status and/or endoscopic findings when determining dosing duration and/or the decision to dose de-escalate. The OCTAVE study reported high clinical response after dose de-escalation to 5 mg twice daily, with 80% and 75% maintaining remission at 2 and 12 months, respectively.[6] However, distinct from our cohort, these patients de-escalated only after having shown clinical and endoscopic remission after 52 weeks on tofacitinib 10 mg twice daily, suggesting that a subset of our cohort may not have yet responded clinically during the induction course. Similarly, in the RIVETING study, more than two thirds of patients who underwent dose de-escalation showed endoscopic remission based on a modified Mayo score at 6 months, of which all were already in stable clinical remission on tofacitinib 10 mg twice daily for at least 6 months before dose de-escalation.[8] An observational retrospective study from the United Kingdom including 134 patients showed that 32% of patients who dose de-escalated showed clinical relapse at a median of 41 days, with another retrospective study noting 42% of patients experiencing clinical relapse after dose reduction.[9,10] Overall, our findings in the context of prior studies suggest that longer periods of remission may be required before tofacitinib dose de-escalation to maintain remission, especially in patients with ongoing clinical and endoscopic disease activity.[6,8,14]

Our cohort included both patients who maintained their induction dose or had dose de-escalation. Notably, we observed similar cumulative rates of UC disease activity–related events through 12 months among both groups, which may be owing to increased UC severity in our cohort. Prior tofacitinib studies included cohorts with fewer than half of patients showing prior tumor necrosis factor inhibitor failure, compared with more than 95% in our cohort, as well as a lower proportion of patients with pancolitis, speaking to the likely increased baseline severity of disease in our cohort.[6,8,9] This was especially evident among patients who maintained their induction dose because they had higher rates of UC-related hospitalizations and were more likely to be steroid-dependent before (67% vs 46%) or during induction (70% vs 50%). In patients who maintained induction dosing, endoscopic evidence of active disease at 6 months after therapy initiation and steroid dependence during the induction period may be important clinical factors to consider when deciding continuation or dose

de-escalation of tofacitinib given their association with a UC event. As such, provider variability is an important factor in choosing which patients to maintain vs dose de-escalate, who may have a perceived higher risk of relapse based on steroid dependence during the induction period.

In addition, we observed that patients who underwent dose de-escalation and had an endoscopic Mayo score of 3 within 6 months of tofacitinib induction were more likely to experience a UC event. Because the decision to dose de-escalate may be based on provider preference given clinical criteria and safety concerns independent from the follow-up endoscopic Mayo score, a sensitivity analysis in a subgroup of non–steroid-dependent patients with evidence of endoscopic improvement (Mayo score, <3) was performed, which showed no difference in the UC event rate based on the duration of the induction course. Similarly, in the RIVETING study, patients in deep remission with an endoscopic score of 0 were more likely to maintain remission after dose de-escalation than those with ongoing disease activity (82% vs 63%), observations that are consistent with dose reduction of other therapy classes.[8,15,16] Thus, emphasis should be placed on clinical and endoscopic evidence of improvement before consideration of dose de-escalation to ensure the highest probability of treatment success.

Currently, per product labeling, tofacitinib induction with 10 mg twice daily beyond 16 weeks is not recommended; in fact, it is recommended to stop after 16 weeks if adequate response has not been achieved.[3] However, patients with an induction period longer than 16 weeks were 63% less likely to experience a UC event after dose de-escalation in our study, suggesting that there may be a subgroup of patients who may benefit from a longer induction course. Prior studies have supported a prolonged induction course, with an additional 8 weeks beyond the first 8 weeks of induction therapy, especially in patients who do not show early clinical response.[11,13,17] Notably, few studies have examined outcomes of induction beyond 16 weeks. Our findings suggest that longer induction periods, even beyond 16 weeks, may benefit patients who otherwise have not yet shown clinical improvement. Concerns of a prolonged induction course largely have been owing to reported VTE events seen in older rheumatoid arthritis patients on 10 mg twice daily.[3–5] Nonetheless, prior post hoc analysis did not show an increased risk in the development of VTE in UC induction or maintenance studies on 10 mg twice daily.[18] In addition, long-term, open-label extension studies showed rare VTE-related events in UC patients, all in those with known VTE risk factors.[6,18,19] In this current study, we observed 2 VTE events. The first was in a patient on a maintenance dose of 5 mg twice daily occurring 8 months after dose initiation, and the second in a patient on 10 mg twice daily in the setting of a peripherally inserted central catheter line, which thus may not have been medication related. Nonetheless, the decision for prolonged induction dosing is an individualized decision between the patient and provider, taking into consideration the patient's clinical status, endoscopic activity, and risk of dose-dependent adverse advents, particularly VTE.

It is important to note that not all patients who underwent dose de-escalation and experienced a UC event were able to recapture clinical response after dose re-escalation. As described in the OCTAVE and prior real-world UK studies, 20% to 35% of patients had a loss of remission despite having a prolonged induction course with clinical/endoscopic evidence of therapy response, with approximately half able to recapture remission after dose re-escalation.[6,9] Notably, more patients (63%) in this study recaptured clinical response, which may have been owing to inadequate drug exposure and ongoing disease at the time of dose de-escalation. Factors observed in the RIVETING trial associated with maintaining remission were deep endoscopic remission and prior tumor necrosis inhibitor failure.[8] In this current study, the degree of active disease on endoscopy was an important contributor to UC events after dose de-escalation after controlling for several patient/disease factors. Notably, we did not observe any difference in rates of UC events after dose de-escalation with prior biologic or small molecule drug exposure. Thus, it is important for providers to carefully consider factors that may predict relapse after de-escalation because not all patients may recapture response.

We acknowledge several potential limitations to our study. First, our cohort was derived from a single tertiary inflammatory bowel disease center including patients who may have more severe disease, as evidenced by disease extent (65% pancolitis) and prior biologic failure (96%), with a mean of 2 prior biologics. As such, our data may not be as generalizable to all UC patients. However, the observed rates of UC events were similar to those reported in prior studies.[6,8,9] Furthermore, it is important to note the potential of selection bias in the allocation of patients within the dose de-escalation or continuation groups because it was based largely on providers' preference and clinical decision derived from therapy monitoring guidance and safety concerns independent from clinical symptoms and/or follow-up endoscopic evaluation. We also acknowledge that timing of dosage adjustment and/or clinical and endoscopic evaluation were not protocolized but rather based on providers' practice patterns, which is a known inherent limitation owing to the nature of this real-world study design. As such, further sensitivity analysis was performed to address this limitation. Baseline and follow-up endoscopic evaluation were not available for every patient and were completed only in patients with ongoing clinical symptoms and/or hospitalizations, thus, this study may have overestimated the prevalence of endoscopic severity and limited confirmation of endoscopic remission before dose de-escalation. Therefore, our primary study outcome of UC disease activity–related events may have included patients with ongoing active disease at the time of follow-up evaluation who might not yet have achieved clinical remission

during induction. Moreover, our small sample size, although comparable with other real-world cohorts, may be subject to type II errors.[11,12] Lastly, our clinical outcome follow-up evaluation was limited to 12 months to maximize the number of primary outcomes and number of patients with available follow-up evaluation. Longer follow-up evaluation is important to further characterize the clinical impact of dose de-escalation on maintenance of clinical remission.

In conclusion, we observed that more than half of patients with moderate to severe UC who underwent tofacitinib dose de-escalation experienced a UC disease activity–related event by 12 months, with nearly two fifths of patients unable to recapture clinical response despite dose re-escalation. Observed factors associated with UC disease activity–related events after dose de-escalation included a shorter induction course of fewer than 16 weeks and active endoscopic disease at 6 months after induction. Providers should consider performing endoscopic assessment before de-escalation, and balance benefits of lower dose and risks of treatment failure, especially in patients with active endoscopic disease, to garner the most benefit from tofacitinib for patients with UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.05.001.

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Conflicts of interest
The authors disclose no conflicts.

Data Availability
The data, analytic methods, and study materials will be made available to other researchers upon request.

Supplementary Table 1. Characteristics of Patients Who Developed Deep Venous Thrombosis After Tofacitinib Initiation

	Patient A	Patient B
Timing of deep venous thrombosis after tofacitinib initiation	8 months	9 months[a]
Dose of tofacitinib	5 mg twice daily	10 mg twice daily
Duration of induction	8 weeks	36 weeks
Sex	Female	Male
Age at time of deep venous thrombosis	19	18
History of prior venous thrombotic events	Yes, prior provoked deep venous thrombosis	No
History of malignancy	No	No
Disease distribution	Pancolitis	Pancolitis
Duration of disease	3 years	2 years
Prior biologic failures, n	3	1
Mayo score before tofacitinib initiation	3	3
Prior/current tobacco use	No	No

[a]In the setting of a peripherally inserted central catheter.

Supplementary Table 2. Baseline and 6-Month Follow-Up Characteristics in Patients With Ulcerative Colitis Disease Activity–Related Event(s) Vs Those Without

	Total, n = 162	Disease activity–related event, n = 93	No event, n = 69	*P* value
Sex, male	87 (54)	49 (53)	38 (55)	.76
Race				.35
White	115 (71)	67 (73)	48 (70)	
Black	2 (1)	2 (2)	0 (0)	
Hispanic	8 (5)	6 (7)	2 (3)	
Asian	21 (13)	9 (10)	12 (17)	
Other	15 (9)	8 (9)	7 (10)	
Body mass index, kg/m^2	24.8 ± 5.5	24.7 ± 5.3	25.0 ± 5.7	.77
Age at diagnosis, *y*	27 (19–35)	27 (20–38)	27 (18–34)	.19
Age at tofacitinib initiation, *y*	35 (28–46)	37 (27–46)	35 (29–44)	.52
Disease duration, *y*	6 (3–13)	6 (2–12)	7 (4–14)	.34
Disease distribution				.89
Proctitis	6 (4)	3 (3)	3 (4)	
Left-sided colitis	50 (31)	28 (30)	22 (32)	
Pancolitis	106 (65)	62 (67)	44 (64)	
Prior biologic failure	155 (96)	91 (98)	64 (93)	.12
Prior biologics failed, n	2.0 ± 1.0	2.0 ± 0.9	2.0 ± 1.1	.13
Hospitalized at time of tofacitinib induction	30 (19)	21 (23)	9 (13)	.12
Therapy in preceding 2 months before tofacitinib				
Corticosteroids	92 (57)	56 (60)	36 (52)	.31
Oral aminosalicylates	18 (11)	12 (13)	6 (9)	.40
Topical therapy	25 (15)	12 (13)	13 (19)	.30
Immunomodulators	32 (20)	19 (20)	13 (19)	.80
Biologics	144 (89)	84 (90)	60 (87)	.50
Stools reported at time of induction, n	8.3 ± 4.2	8.7 ± 4.2	7.7 ± 4.2	.13
Rectal bleeding at induction	111 (72)	67 (76)	44 (66)	.15
Induction Mayo score				.70
0	2 (1)	0 (0)	2 (3)	
1	10 (7)	3 (3)	7 (11)	
2	63 (41)	40 (44)	23 (37)	
3	78 (51)	47 (52)	31 (49)	
De-escalation	78 (48)	44 (47)	34 (49)	.81
Duration of induction course, *wk*				.25
8	28 (17)	20 (22)	8 (12)	
16	27 (17)	15 (16)	12 (17)	
>16	107 (66)	58 (62)	49 (71)	
Therapy during tofacitinib induction				
Corticosteroids	98 (61)	64 (69)	34 (49)	.01
Oral aminosalicylates	12 (7)	7 (8)	5 (7)	.95
Topical therapy	23 (14)	16 (17)	7 (10)	.20
Immunomodulators	4 (3)	2 (2)	2 (3)	1.00
Stools reported at 6 months, n	4.5 ± 3.4	5.7 ± 3.8	2.6 ± 1.4	<.01
Rectal bleeding at 6 months	58 (38)	52 (58)	6 (9)	.07
Mayo score at 6 months				<.01
0	29 (24)	5 (7)	24 (45)	
1	28 (23)	12 (17)	16 (30)	
2	31 (25)	21 (30)	10 (19)	
3	34 (28)	31 (45)	3 (6)	
Physician assessment of clinical response	87 (55)	29 (31)	58 (88)	<.01
Complete endoscopic remission	26 (18)	5 (6)	21 (38)	<.01

NOTE. Values are reported as number (percentage), means ± SD, or median (interquartile range).

Supplementary Table 3. Univariable and Multivariable Cox Regression in Patients With Evidence of Endoscopic Improvement and Noncorticosteroid Dependence in the Setting of Tofacitinib Dose De-Escalation

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex, male	0.51	0.13–1.92	.32	0.50	0.11–2.21	.36
Age at tofacitinib initiation, *y*	0.97	0.91–1.02	.20	0.96	0.91–1.02	.19
Duration of induction course, *wk*						
8	Ref	–	–	Ref	–	–
16	0.47	0.08–2.85	.42	0.74	0.11–5.18	.77
>16	0.63	0.16–2.52	.51	0.98	0.21–4.55	.98

HR, hazard ratio.