Predictors and Outcomes of Ustekinumab Dose Intensification in Ulcerative Colitis: A Multicenter Cohort Study

Rahul S. Dalal,[*] Scott Esckilsen,[‡] Edward L. Barnes,[§] Jordan C. Pruce,[*] Jenna Marcus,[*] and Jessica R. Allegretti[*]

[*]Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [‡]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and [§]Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Ustekinumab has been shown to be effective for the treatment of ulcerative colitis (UC); however, >40% of patients have suboptimal clinical response after induction and maintenance dosing every 8 weeks.[1,2] The best management approach for these patients is unclear. Many undergo empiric dose intensification to every 4 weeks or every 6 weeks, a nonstandardized decision because of limited data supporting therapeutic drug monitoring of ustekinumab.[3] In Crohn's disease, approximately 50% of patients undergo ustekinumab dose intensification, which seems to be effective based on prior work from our group and others.[4-8] However, similar data in UC are lacking. In this real-world multicenter cohort study, we sought to identify predictors and outcomes of ustekinumab dose intensification in UC.

Methods

Study Design

This retrospective cohort study included adults with UC (ICD-10-CM 51x) initiating ustekinumab at Brigham and Women's Hospital, Massachusetts General Hospital, or the University of North Carolina, Chapel Hill between January 1, 2016 and November 1, 2020. Patients with prior colectomy or those treated primarily for non-UC indications were excluded. Electronic health records were reviewed for clinical data. Disease activity was documented using either the simple clinical colitis activity index (SCCAI) or partial Mayo score (Supplementary Methods).

Independent Variables

Independent variables included demographics; UC duration; extraintestinal manifestations; substance use; endoscopic extent/severity; prior/current UC medications; primary documented justification for intensification; intravenous reinduction; dose interval; and the most recent body mass index, albumin, C-reactive protein, and bowel frequency recorded within 12 weeks before intensification (Supplementary Methods).

Outcomes

The primary outcome was corticosteroid-free clinical remission (ie, "remission," SCCAI/Mayo <3 points and no oral/intravenous corticosteroid use for ≥4 weeks) at evaluation 12–16 weeks after intensification. Secondary outcomes were clinical response (ie, "response," reduction in SCCAI/Mayo by ≥3 points from baseline) at 12–16 weeks and time-to-intensification. See the Supplementary Methods for additional end points.

Statistical Analysis

Logistic and Cox proportional hazards regression were used to identify variables associated with remission and time-to-intensification, respectively. Variables with $P < .10$ on univariable analysis were included in multivariable analyses. Covariates with $P < .05$ on multivariable analysis were considered significant (Supplementary Methods).

Results

A total of 108 patients with UC initiated ustekinumab: 56.5% were female, 91.7% had prior anti–tumor necrosis factor exposure, 39.8% had >2 prior biologic exposures, and 57.4% were taking oral corticosteroids (Supplementary Table 1). Among these, 39.6% (40/101 with SCCAI/Mayo data) achieved remission 12–16 weeks after induction.

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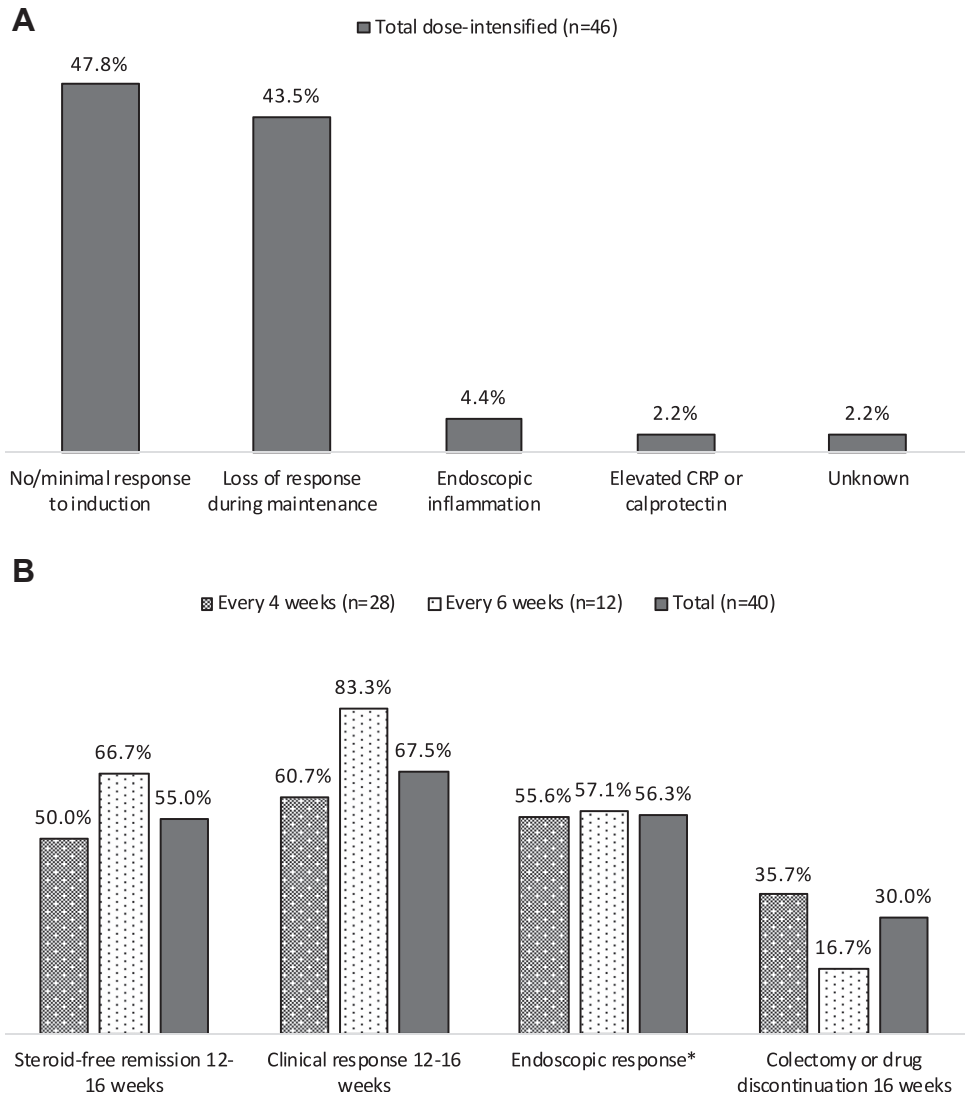

Figure 1. Reasons for dose-intensification (*A*) and outcomes after dose-intensification (*B*). Clinical follow-up data after dose-intensification were available for 40/46 patients. There were no significant differences between every 4 weeks and every 6 weeks outcomes using $P < .05$ by Fisher exact test. *Postintensification endoscopic data were available for n = 9 for every 4 weeks and n = 7 for every 6 weeks. CRP, C-reactive protein.

A total of 42.6% (46/108) required intensification to every 4 weeks (n = 33) or every 6 weeks (n = 13) after a median of 95 days (interquartile range, 65–208 days) primarily for no/minimal response to induction (22/46) or loss of response (20/46) (Figure 1*A*). Intravenous reinduction doses were administered to 4/46 preceding intensification. At 12–16 weeks after intensification, 55.0% (22/40 with SCCAI/Mayo data) achieved remission and 67.5% (27/40) achieved response. Thirty percent (12/40) had drug discontinuation or colectomy within 16 weeks after intensification (Figure 1*B*). Among these, 10/12 had no/minimal response to induction and 2/12 had loss of response. Over a median follow-up of 230 days (interquartile range, 137–623 days) after intensification, 56.3% (9/16 with preintensification/postintensification data) had improvement in endoscopic inflammation and fecal calprotectin (Supplementary Table 2), 10.0% (4/40) had inflammatory bowel disease–related hospitalization, and 5.0% (2/40) had adverse events (urinary tract infection and *Clostridium difficile* infection).

After multivariable analysis, no/minimal response to induction (odds ratio, 0.2; 95% confidence interval, 0.04–0.7) was inversely associated with remission after intensification. Bowel frequency (hazard ratio, 1.1; 95% confidence interval, 1.02–1.2) and >2 prior biologic exposures (hazard ratio, 2.5; 95% confidence interval, 1.1–5.8) were associated with time-to-intensification (Supplementary Table 3).

Discussion

Nearly 40% of UC patients in our multicenter study achieved remission after ustekinumab induction. However >40% required intensification, which was associated with higher daily bowel frequency and >2 prior biologic exposures. Similar to our findings in Crohn's disease,[6] >50% of dose-intensified patients achieved corticosteroid-free remission; however, patients with minimal/no response to induction had lower odds of remission after intensification. We observed no significant differences between every 4 weeks and every 6

weeks dosing; however, larger studies are needed for this comparison.

The strengths of the study include use of an entire multicenter cohort of ustekinumab users to assess predictors and comprehensive outcomes of dose intensification. Limitations include a small sample of dose-intensified patients precluding subgroup analyses. The variability in timing of colonoscopies also limits conclusions regarding endoscopic response. Long-term outcomes are lacking, which is largely caused by the recent Food and Drug Administration approval of ustekinumab for UC in October 2019.

In summary, ustekinumab dose intensification seems to be safe and effective for patients with UC. This strategy may be more effective among patients with loss of response to dosing every 8 weeks rather than those with no response after induction. Prospective studies may identify specific subpopulations that would benefit from different optimization strategies of ustekinumab in 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 https://doi.org/10.1016/j.cgh.2021.03.028.

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Reprint requests
Address requests for reprints to: Jessica R. Allegretti, MD, PhD, 850 Boylston Street, Suite 201, Chestnut Hill, Massachusetts 02467. e-mail: jallegretti@bwh.harvard.edu; fax: (617) 732-9198.

Conflicts of interest
These authors disclose the following: Edward L. Barnes has served as a consultant for AbbVie, Gilead, Pfizer, Takeda, and Target RWE. Jessica R. Allegretti serves as a consultant for Takeda, Janssen, Pfizer, Pandion, Servatus, Finch Therapeutics, Iterative Scopes, and Artugen; and has grant support from Merck. The other authors disclose no conflicts.

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Supplementary Methods

Ethical Consideration

This study was approved by the institutional review boards of Brigham and Women's Hospital and the University of North Carolina, Chapel Hill.

Study Design (Additional Detail)

Clinical disease activity was measured using the SCCAI or partial Mayo score, which are documented in clinic notes in our health system. The SCCAI combines point totals for daytime bowel frequency (0–3 points), nighttime bowel frequency (0–2 points), urgency of defecation (0–3 points), blood in stool (0–3 points), general well-being (0–4 points), and extracolonic manifestations (1 point per manifestation). The partial Mayo score combines point totals for stool frequency (0–3 points), rectal bleeding (0–3 points), and physician global assessment (0–3 points).

Independent Variables (Additional Detail)

Complete list of independent variables includes age; sex; race; ethnicity; UC duration; extraintestinal manifestations; current substance use (cigarettes, cannabis, and opioids); UC disease extent (Montreal classification E1-E3) and severity (Mayo classification 0–3) on most recent colonoscopy; prior biologic exposures; current thiopurines or methotrexate; current oral corticosteroids; primary documented justification for dose intensification per inflammatory bowel disease provider assessment (no/minimal clinical response, loss of response, endoscopic inflammation, elevated biochemical marker, or unknown); intravenous reinduction dose of ustekinumab before dose intensification; dose interval frequency (every 4 weeks or every 6 weeks); and the most recent values of the following continuous variables within 12 weeks before dose intensification: body mass index, serum albumin, C-reactive protein, and daily bowel frequency.

Outcomes (Additional Detail)

Patients who discontinued ustekinumab before 12–16 weeks were considered nonresponders. Some patients ($n = 10$) underwent dose intensification with SCCAI or Mayo score <3 at the time of evaluation, which would not allow them to meet criteria for clinical response after dose intensification (ie, reduction in SCCAI or Mayo score by ≥ 3 points). These individuals reported recurrence/worsening of symptoms at a later point in the treatment cycle (eg, loss of response at week 6 out of 8), prompting dose intensification. For these individuals, clinical response was achieved if they were subsequently able to maintain SCCAI or Mayo score <3 for the full duration of at least 2 treatment cycles after dose intensification and if the inflammatory bowel disease provider documented clinical response in their assessment. Clinical remission was achieved if the same criteria were met in addition to no use of corticosteroids for ≥ 4 weeks at time of the week 12–16 evaluation.

Additional end points included corticosteroid-free clinical remission 12–16 weeks after induction (ie, before dose intensification) and treatment failure within 16 weeks after dose intensification (ustekinumab discontinuation or colectomy because of disease activity). We also assessed improvement in extent or severity of endoscopic inflammation, improvement in fecal calprotectin, UC-related hospitalization, and adverse events or infections at any point after dose-intensification; time restrictions were not assigned to these outcomes because of the limited number of events, therefore these outcomes are intended to be descriptive.

Statistical Analysis (Additional Detail)

Descriptive statistics will be presented as percentages for categorical data and means with standard deviations or medians with interquartile range for continuous data based on the normality of distributions. Univariable logistic regression and Cox regression were used to calculate unadjusted odds ratios and hazards ratios for baseline factors associated with corticosteroid-free remission and time-to-dose intensification, respectively. Variables with 2-tailed $P < .10$ on univariable analysis were included in multivariable analyses. Covariates with $P < .05$ on multivariable analysis were considered significant. For the Cox analysis, patients were censored at loss of follow-up, ustekinumab discontinuation, or colectomy. The proportional hazards assumption was tested using Martingale residuals. Stata/IC versions 15.1 (StataCorp, College Station, TX) was used for all analyses.

Supplementary Table 1. Baseline Characteristics at Ustekinumab Initiation

Baseline characteristics[a]	Fraction (%) or median (IQR)[b]
Female, fraction (%)	61/108 (56.5)
Age, *y*, median (IQR)	39 (30–56)
Disease duration, *y*, median (IQR)	9 (4–16)
BMI, median (IQR)	25.2 (22.9–30.6)
Race, fraction (%)	
White	89/108 (82.4)
Black	7/108 (6.5)
Asian	6/108 (5.6)
Other or unknown	6/108 (5.6)
EIM, fraction (%)	45/108 (41.7)
Prior anti-TNF-α exposure, fraction (%)	99/108 (91.7)
>2 Prior biologic exposures	43/108 (39.8)
Prior immunomodulator, fraction (%)	68/108 (63.0)
Current immunomodulator[c], fraction (%)	18/108 (16.7)
Current corticosteroids[d], fraction (%)	62/108 (57.4)
Current smoking, fraction (%)	6/108 (5.6)
Current cannabis, fraction (%)	15/108 (13.9)
Current opioids, fraction (%)	8/108 (7.4)
SCCAI, median (IQR), n = 63	5 (3–7)
9-Point Mayo, median (IQR), n = 41	4 (2–6)
Daily bowel frequency, median (IQR)	5 (3–8)
Last colonoscopy or sigmoidoscopy	
Montreal disease extent >1	80/108 (74.1)
Mayo endoscopic severity >1	71/107 (66.4)
Last laboratory values, median (IQR)	
Albumin, *g/dL*, n = 99	4.0 (3.8–4.3)
C-reactive protein, *mg/L*, n = 96	3.6 (0.8–12.9)

BMI, body mass index; EIM, extraintestinal manifestation; IQR, interquartile range; SCCAI, simple clinical colitis activity index; TNF, tumor necrosis factor.
[a]Baseline characteristics represent the most recent clinical data available within 12 weeks before ustekinumab initiation, with the exception of last colonoscopy or sigmoidoscopy, which was included with no time limitation.
[b]Total n = 108 unless otherwise specified because of missing data.
[c]Includes azathioprine, 6-mercaptopurine, and methotrexate.
[d]Includes prednisone, methylprednisolone, and oral budesonide preparations.

Supplementary Table 2. Endoscopic and Fecal Calprotectin Data Pre and Post Dose Intensification

Prescope type	Pre- extent	Preseverity	Days scope to intensification	Post-scope type	Postextent	Postseverity	Days intensification to scope	Improvement in extent and/or severity
Colo	3	1	164	Colo	2	1	74	Yes
Colo	2	1	254	Colo	2	1	103	Yes
Sig	1	2	153	Sig	1	1	56	Yes
Colo	3	2	68	Colo	0	0	560	Yes
Colo	2	3	107	Colo	1	1	719	Yes
Colo	2	Missing	444	Colo	1	1	178	Yes
Sig	2	3	402	Colo	0	0	488	Yes
Colo	3	3	53	Colo	0	0	427	Yes
Sig	3	2	437	Colo	2	1	599	Yes
Colo	0	0	243	Sig	2	2	23	No
Colo	2	3	478	Colo	3	3	93	No
Sig	2	1	181	Colo	3	2	55	No
Colo	0	0	952	Colo	0	0	189	No[a]
Colo	3	3	97	Colo	3	3	421	No
Sig	2	2	590	Colo	2	2	55	No
Colo	0	0	1201	Colo	0	0	223	No[a]

Precalprotectin ($\mu g/g$)	Days calprotectin to intensification	Postcalprotectin ($\mu g/g$)	Days intensification to calprotectin	Calprotectin improved
550.6	5	136.3	98	Yes
484.0	103	143.9	157	Yes
89.5	148	<27.1	76	Yes
482.3	55	<27.1	127	Yes
1394.4	119	198.0	34	Yes
163.9	41	<27.1	82	Yes
566.0	5	163.0	130	Yes
>3000	64	2179.6	69	Yes
81.8	3	<27.1	63	Yes
1178.7	10	1356.4	135	No
214.0	131	>1000	189	No
117.3	155	650.1	131	No
35.4	0	519.2	173	No
18.5	135	55.0	305	No
66.4	126	157.4	14	No

NOTE. If patients had multiple preintensification/postintensification endoscopies or calprotectin levels, only those closest in time to dose intensification are included in this table. Extent refers to Montreal disease extent 0–3. Severity refers to endoscopic Mayo subscore 0–3.
Colo, colonoscopy; Sig, flexible sigmoidoscopy.
[a]These patients had endoscopic remission pre and post dose intensification; however, the preintensification endoscopy occurred >1 year before dose intensification.

Supplementary Table 3. Regression Models

Logistic regression covariates for steroid-free remission after dose intensification	Univariable OR (95% CI)	Multivariable OR (95% CI)
No response to induction[a]	0.16 (0.04–0.67)[b]	0.16 (0.04–0.69)[c]
IV reinduction dose	2.68 (0.25–28.31)	
Intensification frequency (every 6 wk vs every 4 wk)	2.0 (0.49–8.20)	
Female	1.81 (0.51–6.36)	
Age, *y*	0.99 (0.95–1.04)	
Disease duration, *y*	1.01 (0.94–1.09)	
Black	0.38 (0.03–4.58)	
BMI	1.07 (0.93–1.23)	
EIM	1.04 (0.30–3.64)	
>2 Prior biologic exposures	0.46 (0.13–1.63)	
Current smoking	—	
Current cannabis	0.50 (0.07–3.38)	
Current opioids	1.70 (0.14–20.42)	
Current corticosteroids	0.29 (0.08–1.06)[b]	0.27 (0.06–1.15)
Current thiopurine or methotrexate	0.44 (0.10–1.92)	
Montreal disease extent >1	1.73 (0.38–7.72)	
Mayo endoscopic severity >1	0.46 (0.11–1.92)	
Daily bowel frequency (preintensification)	0.90 (0.77–1.06)	
Albumin, *g/dL* (preintensification)	2.13 (0.45–10.13)	
C-reactive protein, *mg/L* (preintensification)	1.01 (0.87–1.17)	

Cox covariates for time-to-dose intensification	Univariable HR (95% CI)	Multivariable HR (95% CI)
Female	0.65 (0.30–1.40)	
Age, *y*	0.99 (0.96–1.02)	
Disease duration, *y*	1.01 (0.97–1.05)	
Black race	1.49 (0.35–6.31)	
BMI	0.98 (0.92–1.05)	
EIM	1.08 (0.50–2.33)	
>2 Prior biologic exposures	2.73 (1.26–5.89)[b]	2.53 (1.11–5.81)[c]
Current smoking	—	
Current cannabis	1.57 (0.59–4.21)	
Current opioids	0.41 (0.05–3.01)	
Current corticosteroids	1.94 (0.85–4.43)	
Current thiopurine or methotrexate	1.15 (0.43–3.05)	
Montreal disease extent >1	1.55 (0.59–4.11)	
Mayo endoscopic severity >1	1.32 (0.57–3.02)	
Daily bowel frequency (preinduction)	1.12 (1.03–1.21)[b]	1.10 (1.02–1.20)[c]
Albumin, *g/dL* (preinduction)	0.55 (0.29–1.04)[b]	0.72 (0.35–1.47)
C-reactive protein, *mg/L* (preinduction)	0.99 (0.96–1.01)	

NOTE. Missing values are because of insufficient number of observations.
BMI, body mass index; CI, confidence interval; EIM, extraintestinal manifestation; HR, hazard ratio; IV, intravenous; OR, odds ratio.
[a]Reference group: All other reasons for dose intensification as noted in Figure 1*A*, including loss of response, endoscopic activity, elevated biochemical marker, or unknown.
[b]$P < .10$ on univariable analysis.
[c]$P < .05$ on multivariable analysis.