Supplementary Material

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 IBD provider assessment (no/minimal clinical response, loss of response, endoscopic inflammation, elevated biochemical marker, or unknown), IV reinduction dose of ustekinumab prior to dose

intensification, dose interval frequency (q4w or q6w), and the most recent values of the following continuous variables within 12 weeks prior to dose intensification: body mass index, serum albumin, C-reactive protein, and daily bowel frequency.

Outcomes (additional detail)

Patients who discontinued ustekinumab prior to 12-16 weeks were considered non-responders. 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 (i.e. reduction in SCCAI or Mayo score by ≥3 points). These individuals reported recurrence/worsening of symptoms at a later point in the treatment cycle (e.g. 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 SSCAI or Mayo score < 3 for the full duration of at least 2 treatment cycles after dose intensification and if the IBD 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 endpoints included corticosteroid-free clinical remission 12-16 weeks after induction (i.e. prior to dose intensification) and treatment failure within 16 weeks after dose intensification (ustekinumab discontinuation or colectomy due to 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 due to 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 (ORs) and hazards ratios (HRs) for baseline factors associated with corticosteroid-free remission and time-to-dose intensification, respectively. Variables with two-tailed $p<0.10$ on univariable analysis were included in multivariable analyses. Covariates with $p<0.05$ 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 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 alpha 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)

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

Supplementary Table 2A. Endoscopic and fecal calprotectin data pre- and post- dose intensification

Pre- scope type	Pre-extent	Pre-severity	Days scope to intensification	Post-scope type	Post-extent	Post-severity	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*
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*

Pre-calprotectin (mcg/g)	Days calprotectin to intensification	Post-calprotectin (mcg/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
1,178.7	10	1,356.4	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

If patients had multiple pre/post-intensification endoscopies or calprotectin levels, only those closest in time to dose intensification are included in this table.

*These patients had endoscopic remission pre- and post- dose intensification, however the pre-intensification endoscopy occurred >1 year prior to dose intensification.

Colo = colonoscopy, Sig = flexible sigmoidoscopy, extent refers to Montreal disease extent 0-3, severity refers to endoscopic Mayo subscore 0-3

Supplementary Table 2B. 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 (q6w vs q4w)	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 (pre-intensification)	0.90 (0.77-1.06)	
Albumin, g/dL (pre-intensification)	2.13 (0.45-10.13)	
C-reactive protein, mg/L (pre-intensification)	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 (pre-induction)	1.12 (1.03-1.21)[b]	1.10 (1.02-1.20)[c]
Albumin, g/dL (pre-induction)	0.55 (0.29-1.04)[b]	0.72 (0.35-1.47)
C-reactive protein, mg/L (pre-induction)	0.99 (0.96-1.01)	

[a]Reference group: All other reasons for dose intensification as noted in Figure 1A, including loss of response, endoscopic activity, elevated biochemical marker, or unknown

[b]$p<0.10$ on univariable analysis

[c]p<0.05 on multivariable analysis
Missing values are due to insufficient number of observations
Abbreviations: BMI = body mass index, EIM = extraintestinal manifestation, HR = hazard ratio, OR = odds ratio