Delayed Ustekinumab Responders in Ulcerative Colitis Have Greater Inflammatory Burden but Similar Outcomes as Early Responders

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BACKGROUND & AIMS: **Differences in 1-year outcomes among early compared with delayed responders to vedolizumab have been shown in ulcerative colitis. However, it is unclear whether similar differences exist with ustekinumab, and what factors differentiate delayed responders from nonresponders.**

METHODS: **This study was a post hoc analysis of patient-level data from the UNIFI clinical trial. Ustekinumab-treated patients with clinical response, defined as a reduction in total Mayo score of 30% or more and 3 or more points from baseline with a reduction in their rectal bleeding subscore of 1 or more or a rectal bleeding subscore of 1 or less, at week 8 were deemed early responders and their outcomes were compared with delayed responders (week 8 nonresponders who subsequently responded at week 16). The primary outcome assessed was 1-year clinical remission, defined as a total Mayo score of 2 or less and no subscore greater than 1.**

RESULTS: **We included 642 ustekinumab-treated patients, including 321 (50%) early responders, 115 (17.9%) delayed responders, and 205 (32.1%) nonresponders. No differences were observed for 1-year clinical remission among early vs delayed responders (132 of 321 [41.1%] vs 40 of 115 [34.8%]; $P = .233$), or for other outcomes assessed regardless of induction dose. Compared with early responders, delayed responders had more severe baseline Mayo endoscopic disease (88 of 115 [76.5%] vs 206 of 321 [64.2%]; $P = .015$) and abnormal baseline C-reactive protein level greater than 3 mg/L (83 of 115 [72.2%] vs 183 of 321 [57%]; $P = .004$). Compared with nonresponders, delayed responders had a significant decrease in C-reactive protein level (F-value [degrees of freedom, mean squares] [4, 844]; $P < .0001$) and fecal calprotectin level (F[4, 818]; $P < .0001$) through week 16.**

CONCLUSIONS: **Compared with early ustekinumab responders, delayed responders had a greater inflammatory burden at baseline. Early and delayed responders had similar 1-year outcomes. Biomarker decline observed in delayed responders can help differentiate them from nonresponders.**

Keywords: Ulcerative Colitis; Ustekinumab; Response; Inflammatory Bowel Disease; Endoscopic Improvement.

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that affects the large intestine.[1] With several approved therapeutic options with various modes of action for treating moderate to severely active UC, positioning of therapies is increasingly important. A key consideration when positioning UC treatments is the rapidity of response based on symptoms and endoscopy. Although some therapies have shown symptom improvement as soon as 1 to 3 days after initiation,[2,3] clinicians often wait several weeks to months before determining whether an advanced therapy is effective for a patient. This practice has largely been adapted because of clinical trial programs showing that nonresponders to induction therapy may have a clinical response when therapy is continued for an additional several weeks or months.[4–7] However, in these patients in whom symptom

Abbreviations used in this paper: **ANOVA, analysis of variance; CR, clinical remission; CRP, C-reactive protein; HEMI, histo-endoscopic mucosal improvement; IQR, interquartile range; MES, Mayo endoscopic subscore; PMS, partial Mayo score; PRO, patient-reported outcome; UC, ulcerative colitis.**

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improvement appears to be delayed, there is a risk of extended exposure to steroids, prolonged inconvenience in quality of life, truancy from work or school, and an increased risk of disease-related complications such as infections or thromboembolism while they remain unwell.[8,9] Furthermore, it has been observed with vedolizumab that the response observed in delayed remitters may not be as durable as that seen with early responders.[10]

Although entry into the maintenance portion of clinical trials for UC typically excludes induction nonresponders, the multicenter, double-blind, placebo-controlled phase 3 UNIFI study (ClinicalTrials.gov identifier: NCT02407236) is one example in which week 8 nonresponders to ustekinumab received an additional dose of ustekinumab subcutaneously (90 mg) in a blinded manner and response was assessed subsequently at week 16.[11] Participants who responded were deemed delayed responders and permitted entry into the maintenance trial. However, it is unclear what specific baseline factors are associated with delayed response to ustekinumab, and, furthermore, whether differences in long-term outcomes among early vs delayed responders exist as shown previously with vedolizumab.[10] Accordingly, we performed a post hoc analysis of data from the UNIFI study to compare longer-term efficacy between UC patients who attain early and delayed response to ustekinumab, and to identify characteristics that could be used by clinicians in identifying patients who are more likely to require prolonged ustekinumab and differentiate them from patients who are nonresponders to therapy.

What You Need to Know

Background

Differences in outcomes have been observed among early and delayed responders to vedolizumab in ulcerative colitis, although it is unclear if this is true for ustekinumab.

Findings

Compared with early responders, delayed responders to ustekinumab had greater inflammatory burden at baseline, although both had similar 1-year outcomes.

Implications for patient care

Consideration should be given to a strategy of waiting for a response among initial nonresponders, and biomarker monitoring can be helpful to differentiate delayed responders from nonresponders.

Methods

We performed a post hoc analysis of patient-level clinical trial data from the UNIFI study obtained through the Yale University Open Data Access Project (#2022-4960) and by permission from Janssen, Inc.[12] The Hamilton Integrated Research Ethics Board determined that local ethics review was not required because data were collected previously and deidentified data were being used, therefore no informed consent was required.

Participants

Details regarding the design and eligibility criteria of the UNIFI study have been published previously.[11] Moderate to severely active UC patients were randomized to receive placebo or ustekinumab intravenously for induction at either a dose of 6 mg/kg or 130 mg once. Clinical response was measured at week 8 and defined as a reduction in total Mayo score of 30% or greater and 3 or more points from baseline including a 1 point or larger reduction in the rectal bleeding subscore or a rectal bleeding subscore of 1 or less. Those who did not meet clinical response criteria with ustekinumab subsequently received ustekinumab 90 mg subcutaneously in a blinded manner, while nonresponders to placebo received a dose of 6 mg/kg of ustekinumab intravenously and both groups were monitored for another 8 weeks. At week 16, patients were re-assessed, and those with a response after not having a response to induction were deemed delayed responders. Week 8 responders were rerandomized into the maintenance portion of the trial, while delayed responders entered the maintenance trial but were not rerandomized and were assigned ustekinumab 90 mg subcutaneously every 8 weeks, with blinding to treatment maintained throughout the trial for all participants. Nonresponders at week 16 were discontinued from the remainder of the trial. Endoscopy with biopsy was performed at the end of induction (week 8) and at the end of maintenance (week 52), with an additional week 16 endoscopy performed in patients who did not respond at week 8.

For this analysis, participants who achieved clinical response at week 8 are herein referred to as early responders, while nonresponders at week 8 who subsequently responded at week 16 are delayed responders. Nonresponders were those who did not respond at week 8 or week 16. Sensitivity analyses were planned using an alternative definition response based on the partial Mayo score (PMS), defined as a PMS of 1 or less because this definition was used in prior studies evaluating delayed response using vedolizumab.[10]

Outcomes

The primary outcome of interest was clinical remission (CR) at week 52, defined as a total Mayo score of 2 or less and no subscore greater than 1. Alternate definitions for clinical remission also were evaluated including the Adapted Mayo Score clinical remission

(stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore of 0, and Mayo endoscopic subscore [MES] ≤1) and patient-reported outcome (PRO)-2 item remission (rectal bleeding and stool frequency subscores, 0). Secondary outcomes including comparisons of 1-year endoscopic improvement (MES, 0 or 1), endoscopic remission (MES, 0), and histo-endoscopic mucosal improvement (HEMI) (MES, ≤1; Geboes score highest grade, <3.2).

Statistical Analysis

Descriptive statistics were calculated and presented as means with SDs or medians with interquartile ranges (IQR). Differences in baseline variables between groups were assessed using *t* tests, analysis of variance (ANOVA), or the Mann–Whitney *U* test. We hypothesized that patients with increased inflammatory burden as measured by the MES were more likely to require additional ustekinumab dosing before responding. Exploratory analyses comparing biomarkers were planned to better understand the impact of inflammatory burden. To determine if changes in biomarker levels over time differed among nonresponders and delayed responders, a 1-way repeated-measures ANOVA was used. Lines of best fit were plotted and slopes were compared using *t* tests comparing interaction terms in the model.[13] A *P* value threshold of less than .05 indicated statistical significance. Several secondary outcomes also were assessed for hypothesis generation using the same *P* value threshold.

Results

A total of 642 ustekinumab-treated participants were included in the current analysis, of whom 321 (50%) were early responders, 115 (17.9%) were delayed responders, and 205 (32.1%) were nonresponders. Table 1 shows the baseline characteristics of participants stratified by induction response. Compared with early responders, delayed responders had more severe endoscopic disease as measured by the MES (88 of 115 [76.5%] vs 206 of 321 [64.2%]; $P = .015$), mean ulcerative colitis endoscopic index of severity (4.8 [SD, 1.2] vs 4.4 [SD, 1.2]; $P < .001$), and the presence of bleeding based on the ulcerative colitis endoscopic index of severity (100 of 115 [87%] vs 245 of 321 [76.3%]; $P = .016$). The median C-reactive protein (CRP) level also was increased among delayed compared with early responders (5.8 mg/L [IQR, 2.5–13.2] vs 3.9 mg/L [IQR, 1.5–11.6]; $P = .011$), and more delayed responders had an abnormal CRP level at baseline based on a threshold greater than 3 mg/L (83 of 115 [72.2%] vs 183 of 321 [57%]; $P = .004$). Baseline characteristics were increased similarly among nonresponders as they were among delayed responders (Table 1). No other baseline variables assessed were significantly different between early and delayed responders. Notably, prior biologic failure was similar between early and delayed responders (142 of 321 [44.2%] vs 48 of 115 [41.7%]; $P = .643$).

Comparison of 1-Year Outcomes in Early Vs Delayed Responders to Ustekinumab

Table 2 reports outcomes at 1 year among early and delayed responders. No differences were observed for 1-year CR (132 of 321 [41.1%] vs 40 of 115 [34.8%]; $P = .233$). Similarly, using alternative definitions for CR, no differences were observed between early and delayed responders for adapted Mayo score CR (144 of 321 [44.9%] vs 43 of 115 [37.4%]; $P = .165$) or PRO-2 remission (121 of 321 [37.7%] vs 37 of 115 [32.2%]; $P = .291$). With regard to endoscopic improvement, no significant differences were observed in early compared with delayed responders (152 of 321 [47.4%] vs 46 of 115 [40.0%]; $P = .174$). There also were no differences seen between the 2 groups with regard to endoscopic remission (84 of 321 [26.2%] vs 27 of 115 [23.5%]; $P = .570$) or HEMI (142 of 321 [44.2%] vs 43 of 115 [37.4%]; $P = .203$).

When PMS response was assessed, a total of 178 patients were considered early responders and 94 were considered delayed responders. Again, no significant differences were observed for 1-year CR (89 of 178 [50%] vs 50 of 94 [53.2%]; $P = .617$), adapted Mayo score CR (94 of 178 [52.8%] vs 50 of 94 [53.2%]; $P = .952$), PRO-2 remission (101 of 178 [56.7%] vs 51 of 94 [54.3%]; $P = .695$), endoscopic improvement (95 of 178 [53.4%] vs 50 of 94 [53.2%]; $P = .978$), endoscopic remission (59 of 178 [33.2%] vs 34 of 94 [36.2%]; $P = .617$), or HEMI (90 of 178 [50.6%] vs 48 of 94 [51.1%]; $P = .937$) (Supplementary Table 1).

Impact of Induction Dose on 1-Year Outcomes Among Delayed Responders to Ustekinumab

Of the 115 patients who were deemed delayed responders to ustekinumab, a total of 70 of 115 (60.9%) received a weight-based (6 mg/kg) dose of ustekinumab compared with 45 of 115 (39.1%) who received a fixed (130 mg) dose of ustekinumab. Outcomes at 1 year were similar among delayed responders who received a weight-based vs fixed induction dose of ustekinumab for CR (26 of 70 [37.1%] vs 14 of 45 [31.1%]; $P = .507$), adapted Mayo score CR (26 of 70 [37.1%] vs 17 of 45 [37.8%]; $P = .945$), or PRO-2 remission (21 of 70 [30.0%] vs 16 of 45 [35.6%]; $P = .534$). Endoscopic and histologic outcomes were similar at 1 year when endoscopic improvement (27 of 70 [38.6%] vs 19 of 45 [42.2%]; $P = .697$), endoscopic remission (17 of 70 [24.3%] vs 10 of 45 [22.2%]; $P = .799$), and HEMI (25 of 70 [35.7%] vs 18 of 45 [40.0%]; $P = .643$) were assessed (Table 3).

Table 1. Baseline Characteristics of UNIFI Participants Stratified by Induction Response

	Early responder (n = 321)	Delayed responder (n = 115)	Nonresponder (n = 206)	*P* value (pairwise early vs delayed)	*P* value (pairwise delayed vs nonresponder)
Age, *y*, means (SD)	34.1 (14.8)	37.8 (14.4)	35.6 (15.0)	.021	.503
Weight, *kg*, median (IQR)	72.8 (60.7–85.5)	74.0 (62.5–87.5)	74.0 (62.1–84.0)	.413	.745
Height, *cm*, median (IQR)	1.7 (1.6–1.8)	1.7 (1.6–1.8)	1.7 (1.6–1.8)	.071	.072
BMI, median (IQR)	25.0 (21.7–28.1)	24.8 (21.9–28.4)	24.8 (21.6–28.2)	.587	.840
BMI category				.739	.734
Underweight/normal weight, BMI, <25	156 (49.1)	60 (52.2)	110 (53.4)		
Overweight, BMI, ≥25 to <30	118 (37.1)	38 (33.0)	71 (34.5)		
Obese, BMI, ≥30	44 (13.8)	17 (14.8)	25 (12.1)		
Male, n (%)	175 (54.5)	69 (60.0)	141 (68.5)	.310	.255
Caucasian, n (%)	291 (90.7)	109 (94.8)	185 (89.8)	.168	.435
Prior biologic failure, n (%)	142 (44.2)	48 (41.7)	138 (67.0)	.643	.358
Prior vedolizumab use, n (%)	48 (15.0)	15 (13.0)	58 (28.2)	.617	<.001
Prior anti-TNF use, n (%)	94 (29.3)	33 (28.7)	80 (38.8)	.905	.071
Disease duration, *y*, means (SD)	5.5 (3.6)	5.9 (3.9)	5.3 (2.9)	.381	.638
Disease extent, n (%)				.139	.243
Left-sided or proctosigmoiditis	184 (57.3)	75 (65.2)	92 (44.7)		
Pancolitis	137 (42.7)	40 (34.8)	114 (55.3)		
Concomitant immunomodulator use, n (%)	46 (14.3)	22 (19.1)	30 (14.6)	.223	.856
Concomitant mesalamine use, n (%)	141 (43.9)	52 (45.2)	81 (39.3)	.811	.711
Concomitant corticosteroid use, n (%)	109 (34.0)	37 (32.2)	76 (36.9)	.728	.564
Baseline Mayo score, means (SD)	9.0 (1.5)	9.3 (1.5)	8.6 (1.6)	.097	.271
Baseline partial Mayo score, means (SD)	6.3 (1.3)	6.5 (1.3)	5.8 (1.5)	.213	.500
Baseline Mayo endoscopic subscore, n (%)				.015	.056
2	115 (35.8)	27 (23.5)	48 (23.3)		
3	206 (64.2)	88 (76.5)	158 (76.7)		
Baseline CRP level, *mg/L*, median (IQR)	3.9 (1.5–11.6)	5.8 (2.5–13.2)	5.1 (2.2–13.2)	.011	.062
Baseline CRP level >3 mg/L, n (%)	183 (57.0)	83 (72.2)	143 (69.4)	.004	.242
Baseline albumin level, *g/L*, median (IQR)	42.0 (39.0–44.0)	42.0 (38.0–44.0)	42.0 (39.0–44.0)	.917	.856
Baseline albumin level <40 g/L, n (%)	86 (26.8)	39 (33.9)	66 (32.0)	.147	.354
Baseline fecal calprotectin level, *mcg/g*, median (IQR)	1501.5 (548–3032.5)	1371 (602–3311)	1453 (601–2687)	.596	.745
Baseline fecal calprotectin level >250 mcg/g, n (%)	297 (92.5)	101 (87.8)	192 (93.2)	.125	.253
Baseline UCEIS, means (SD)	4.4 (1.2)	4.8 (1.2)	4.7 (1.2)	<.001	.779
Presence of friability, n (%)	272 (84.7)	99 (86.1)	184 (89.3)	.727	.823
Vascular pattern (UCEIS)				.565	.654
0 = Normal	1 (0.3)	0	1 (0.5)		
1 = Patchy obliteration	65 (20.3)	19 (16.5)	34 (16.5)		
2 = Obliterated	255 (79.4)	96 (83.5)	171 (83.0)		
Bleeding (UCEIS)				.062	.092
0 = None	76 (23.7)	15 (13.0)	43 (20.9)		
1 = Mucosal	193 (60.1)	80 (69.6)	129 (62.6)		
2 = Luminal mild	47 (14.6)	16 (13.9)	29 (14.1)		
3 = Luminal moderate to severe	5 (1.6)	4 (3.5)	5 (2.4)		

Table 1. Continued

	Early responder (n = 321)	Delayed responder (n = 115)	Nonresponder (n = 206)	*P* value (pairwise early vs delayed)	*P* value (pairwise delayed vs nonresponder)
Bleeding (UCEIS), any vs none	245 (76.3)	100 (87.0)	163 (79.1)	.016	.032
Erosions/ulcerations (UCEIS)				.063	.153
0 = None	3 (0.9)	1 (0.9)	1 (0.5)		
1 = Erosions	112 (34.9)	27 (23.5)	48 (23.3)		
2 = Superficial ulcer	185 (57.6)	73 (63.5)	139 (67.5)		
3 = Deep ulcer	21 (6.5)	14 (12.2)	18 (8.7)		
Erosions/ulcerations (UCEIS) deep vs not (superficial or erosions)				.057	.074
Basal plasmacytosis[a]				.940	.643
0 = None	63 (25.7)	23 (24.0)	35 (20.2)		
1 = Focal	81 (33.1)	33 (34.4)	55 (31.8)		
2 = Diffuse	101 (41.2)	40 (41.7)	83 (48.0)		
Erosions/ulcerations[b]				.356	.174
0 = No erosion, ulceration, or granulation tissue	50 (17.2)	20 (18.4)	20 (10.3)		
1 = Recovering epithelium and adjacent inflammation	84 (28.9)	22 (20.2)	52 (26.7)		
2 = Probable erosion focally stripped	71 (24.4)	25 (22.9)	36 (18.5)		
3 = Unequivocal erosion	66 (22.7)	32 (29.4)	66 (33.9)		
4 = Ulcer or granulation tissue	20 (6.9)	20 (6.9)	21 (10.8)		
Crypt destruction[c]				.118	.243
0 = None	77 (27.5)	30 (28.9)	52 (28.1)		
1 = Probable, local excess of neutrophils in part of crypt	92 (32.9)	23 (22.1)	47 (25.4)		
2 = Probable, marked attenuation	55 (9.6)	30 (28.9)	42 (22.7)		
3 = Unequivocal crypt destruction	56 (20.0)	21 (20.2)	44 (23.8)		
Neutrophils in epithelium[b]				.647	.654
0 = None	35 (12.5)	15 (14.4)	19 (10.3)		
1 = <5% crypts involved	52 (18.6)	14 (13.5)	30 (16.2)		
2 = <50% crypts involved	113 (40.4)	46 (44.2)	75 (40.5)		
3 = >50% crypts involved	80 (28.6)	29 (27.9)	61 (33.0)		
Neutrophils in lamina propria[b]				.096	.324
0 = No increase	30 (10.3)	14 (12.8)	18 (9.2)		
1 = Mild but unequivocal increase	127 (43.8)	33 (30.3)	68 (34.9)		
2 = Moderate increase	119 (41.0)	57 (52.3)	96 (49.2)		
3 = Marked increase	14 (4.8)	5 (4.3)	13 (6.7)		
Eosinophils in lamina propria[b]				.379	.235
0 = No increase	52 (17.9)	18 (16.5)	42 (21.5)		
1 = Mild but unequivocal increase	150 (51.7)	63 (57.8)	105 (53.9)		
2 = Moderate increase	82 (28.3)	28 (25.7)	46 (23.6)		
3 = Marked increase	6 (2.1)	0	2 (1.0)		
Chronic inflammation[b]				.357	.654
0 = No increase	5 (1.7)	3 (2.8)	4 (2.1)		
1 = Mild but unequivocal increase	52 (17.9)	16 (14.7)	24 (12.3)		
2 = Moderate increase	148 (51.0)	49 (45.0)	89 (45.6)		
3 = Marked increase	85 (29.3)	41 (37.6)	78 (40.0)		
Structural/architectural changes[b]				.544	.563
0 = No abnormality	4 (1.4)	2 (1.8)	3 (1.5)		
1 = Mild abnormality	69 (23.8)	21 (19.3)	14 (7.2)		
2 = Mild or moderate diffuse or multifocal abnormalities	123 (42.4)	43 (39.5)	89 (45.6)		
3 = Severe diffuse or multifocal abnormalities	94 (32.4)	43 (39.5)	89 (45.6)		

Table 1. Continued

	Early responder (n = 321)	Delayed responder (n = 115)	Nonresponder (n = 206)	*P* value (pairwise early vs delayed)	*P* value (pairwise delayed vs nonresponder)
Baseline ustekinumab trough level, *μg/mL*, means (SD)	91.8 (48.1)	76.7 (44.7)	84.0 (47.3)	.011	.067

BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity.
[a]Among 514 patients with available data.
[b]Among 594 patients with available data.
[c]Among 569 patients with available data.

Biomarker Trends in Delayed Responders and Nonresponders

Figure 1 shows CRP trends through week 16 in delayed responders and nonresponders. Compared with nonresponders, delayed responders experienced a significant decrease in CRP (F-value [degrees of freedom, mean squares] [4, 844]; $P < .0001$) based on 1-way repeated-measures ANOVA, with the slope of the line of best fit for nonresponders being almost flat (0.06). Figure 2 shows fecal calprotectin trends through week 16 in delayed responders and nonresponders. Although both lines of best fit had a declining slope, there was significantly larger decline in fecal calprotectin observed among delayed responders compared with nonresponders (F[4, 818]; $P < .0001$) through week 16 based on 1-way repeated-measures ANOVA.

Discussion

In this post hoc analysis, we observed that patients with moderate to severe UC who are delayed responders to ustekinumab had a greater baseline inflammatory burden. Our findings suggest that a strategy for waiting an additional 8 weeks (ie, a total of 16 weeks of treatment) may be of benefit to patients with severe endoscopic disease and/or increased CRP levels. Balancing the potential risks and benefits of waiting for a response poses a particular challenge to clinicians. For some patients with a greater inflammatory burden, an additional dose of ustekinumab may be required and could mean the difference between premature treatment discontinuation or attaining disease control with ustekinumab. Early discontinuation often is met with resistance by clinicians owing to possible development of immunogenicity and a perceived inability to reintroduce an agent as a result.[14] On the other hand, waiting an additional 8 weeks for a response may prolong patient suffering on inefficacious therapy and potentially lead to disease-related complications such as infections or venous thromboembolism resulting from persistently active disease. Furthermore, the proportion of patients achieving 1-year remission among delayed responders to ustekinumab was similar to those who were considered early responders at week 8. This further supports the strategy of waiting for a delayed response to ustekinumab when appropriate.

Although we observed that a greater proportion of patients with severe endoscopic disease and/or

Table 2. Outcomes at 1 Year Among Early Vs Delayed Responders

One-year outcome, n (%)	Early responder (n = 321)	Delayed responder (n = 115)	*P* value
Clinical remission, total Mayo score ≤2 and no subscore >1	132 (41.1)	40 (34.8)	.233
Adapted Mayo score clinical remission, SF subscore ≤1 but not greater than baseline, RB subscore of 0, and MES ≤1	144 (44.9)	43 (37.4)	.165
PRO-2 remission, SF and RB subscore of 0	121 (37.7)	37 (32.2)	.291
Endoscopic improvement, MES ≤ 1	152 (47.4)	46 (40.0)	.174
Endoscopic remission, MES = 0	84 (26.2)	27 (23.5)	.570
Histo-endoscopic mucosal improvement, Geboes highest grade <3.2 and MES ≤1	142 (44.2)	43 (37.4)	.203

MES, Mayo endoscopic subscore; PRO, patient-reported outcome; RB, rectal bleeding; SF, stool frequency.

Table 3. Outcomes at 1 Year Among Delayed Responders Stratified by Weight-Based Vs Fixed Induction Doses of Ustekinumab

One-year outcome, n (%)	Weight-based, 6 mg/kg (n = 70)	Fixed, 130 mg (n = 45)	*P* value
Clinical remission, total Mayo score ≤2 and no subscore >1	26 (37.1)	14 (31.1)	.507
Adapted Mayo score clinical remission, SF subscore ≤1 but not greater than baseline, RB subscore of 0, and MES ≤1	26 (37.1)	17 (37.8)	.945
PRO-2 remission, SF and RB subscore of 0	21 (30.0)	16 (35.6)	.534
Endoscopic improvement, MES ≤1	27 (38.6)	19 (42.2)	.697
Endoscopic remission, MES = 0	17 (24.3)	10 (22.2)	.799
Histo-endoscopic mucosal improvement, Geboes highest grade <3.2 and MES ≤1	25 (35.7)	18 (40.0)	.643

MES, Mayo endoscopic subscore; PRO, patient-reported outcome; RB, rectal bleeding; SF, stool frequency.

increased CRP level were delayed responders, notably these characteristics were similar to those shown among nonresponders, which may suggest additional factors beyond inflammatory burden that may distinguish delayed responders and nonresponders. Future studies investigating markers of nonresponse and delayed response are needed to improve our understanding of this phenomenon. Despite greater inflammatory burden at baseline among delayed responders, outcomes at 1 year were similar to early responders. This could suggest long-term outcomes with ustekinumab are favorable regardless of time to response during induction, although further validation is necessary. Compared with other intravenous biologic options, it remains plausible that ustekinumab has a slower onset of efficacy in alleviating symptoms in moderate–severe UC. As a monoclonal antibody targeting interleukin 12 and interleukin 23, ustekinumab binds to receptors on cells of the innate immune system and lead to downstream differentiation of T-helper cells, thus activating the type 1 T helper pathway. UC is thought to be mediated largely by the type 2 T helper pathway, and different cytokine profiles have been noted.[15] However, these observations were limited to studies performed at single institutions, and larger multicenter studies with adequate statistical power are needed to further understand this phenomenon.

In VARSITY, participants who were early responders to vedolizumab but not adalimumab had favorable outcomes at week 52 compared with delayed responders. This is in contrast to the trends observed in our study. There are several plausible reasons worth noting. First, ustekinumab may have a slower onset of action compared with vedolizumab. Second, differences in trial design may be contributory because patients were blinded to ustekinumab if they did not respond at week 8. Therefore, participants and investigators were unaware if they were receiving active therapy. This is in comparison with

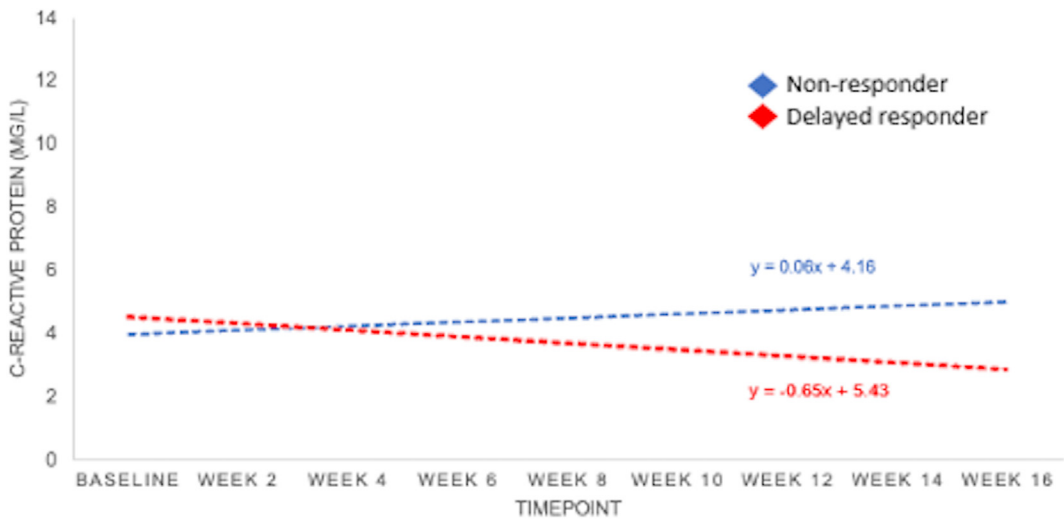

Figure 1. Median C-reactive protein levels through week 16 among ustekinumab delayed responders vs nonresponders.

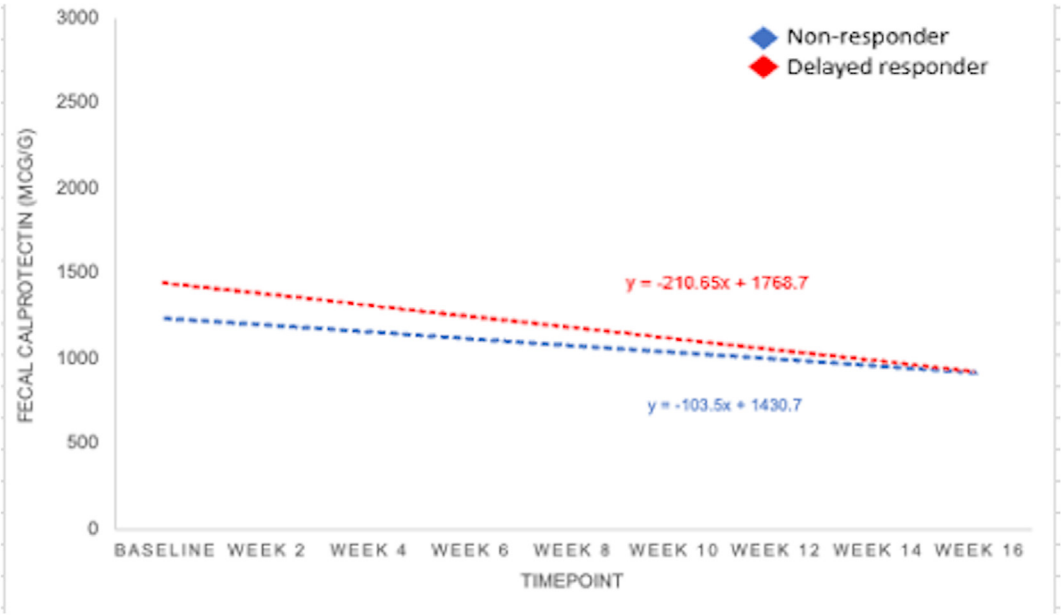

Figure 2. Median fecal calprotectin levels through week 16 among ustekinumab delayed responders vs nonresponders.

VARSITY, in which patients were aware that they were receiving active therapy (either vedolizumab or adalimumab). In general, patients who are aware that they are receiving active therapy are more likely to report a symptomatic response, and this likely is why response rates for vedolizumab and adalimumab are higher in VARSITY compared with GEMINI-1 or ULTRA-2.

In clinical practice, it may be challenging to differentiate a delayed responder from a nonresponder, and use of biomarkers may be helpful with this decision. We observed that there were significant differences in calprotectin and CRP level trends in delayed responders compared with nonresponders. In particular, CRP levels generally remained flat in nonresponders but continued to decline over 16 weeks in delayed responders. Fecal calprotectin level declines were observed in both nonresponders and delayed responders, but the decline was more pronounced in delayed responders. Close monitoring of biomarkers at weeks 4 and 8 could assist clinicians when determining whether more time and an additional dose of ustekinumab may be appropriate for UC patients who received an induction dose of ustekinumab. Biomarkers play a pivotal role in not only the assessment of therapeutic effect, but also the prediction of outcomes among patients with UC. Although endoscopy remains the gold standard to assess disease activity in UC, biomarkers can be used with greater frequency without additional burden to the patient. As such, early identification of patients for which a strategy of waiting for a delayed response could be beneficial, reducing patient burden and costs.

Prior studies with other therapeutic classes have suggested that patients with biologic failure may need to wait longer for a response.[16] However, we observed similar rates of prior biologic failure among early and delayed responders, which suggests an additional period of waiting based solely on prior biologic failure may not be necessary when treating with ustekinumab.

Our study had several strengths, including the use of a high-quality, phase 3, clinical trial data set; blinded central scoring for endoscopic and histologic outcome assessments; and consistency of observations for all outcomes compared. Furthermore, the UNIFI clinical trial study design in which initial nonresponders were offered an additional week 8 dose in a blinded manner helped mitigate bias associated with receiving open-label therapy. However, several limitations are worth noting. Although none of the outcomes between early and delayed responders evaluated in this study were statistically significant, most outcomes appeared to numerically favor early responders, which could lead to type II error when concluding that both of these groups had similar outcomes. This analysis was unable to capture the consequences of not responding and whether that led to additional patient-related complications, colectomies, or truancy from work and school. Furthermore, although we did not observe any baseline differentiating factors between early and delayed responders, the long-term benefit beyond 1 year of this strategy of additional waiting remains unclear. In addition, initial nonresponders were assigned ustekinumab for an additional 8 weeks, and blinding was maintained. Therefore, assessment of 1-year CR and adapted Mayo score CR, which largely are patient-reported outcomes, were unbiased by patient awareness of receiving active treatment. This study was intended to be hypothesis-generating and additional studies are needed to confirm our findings with other advanced therapies.

In summary, we observed that ustekinumab-treated patients with a delayed response have greater

inflammatory burden compared with those with an early response. Our study provides evidence underscoring the importance of inflammatory burden, and may help to appropriately set expectations of clinicians and patients when determining when to expect clinical response to ustekinumab when treating those with greater inflammatory burden. For some patients, it is worthwhile to persist with additional dosing because longer-term outcomes appear comparable for delayed and early responders. Use of biomarker monitoring may be helpful for determining for which patients to persist with additional dosing. The decision to wait for a response ultimately should be made given the totality of evidence in which the benefits of waiting outweigh the risks.

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.2023.06.011.

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Conflicts of interest
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Supplementary Table 1. Outcomes at 1 Year Among Early Vs Delayed Responders Based on Partial Mayo Score Response

One-year outcome, n (%)	Early responder (n = 178)	Delayed responder (n = 94)	*P* value
Clinical remission, total Mayo score ≤2 and no subscore >1	89 (50.0)	50 (53.2)	.617
Adapted Mayo score clinical remission, SF subscore ≤1 but not greater than baseline, RB subscore of 0, and MES ≤1	94 (52.8)	50 (53.2)	.952
PRO-2 remission, SF and RB subscore of 0	101 (56.7)	51 (54.3)	.695
Endoscopic improvement, MES ≤1	95 (53.4)	50 (53.2)	.978
Endoscopic remission, MES = 0	59 (33.2)	34 (36.2)	.617
Histo-endoscopic mucosal improvement, Geboes highest grade <3.2 and MES ≤1	90 (50.6)	48 (51.1)	.937

NOTE. Partial Mayo score response was defined as PMS ≤1 at week 16 (but not in PMS remission at week 8).
MES, Mayo endoscopic subscore; PRO, patient-reported outcome; RB, rectal bleeding; SF, stool frequency.