Post-Induction High Adalimumab Drug Levels Predict Biological Remission at Week 24 in Patients With Crohn's Disease

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INTRODUCTION: **We investigated whether early adalimumab drug levels (ADL) at week 4 predicted biological remission at week 24.**

METHODS: **In a prospective study, we assessed clinical and biological remission at weeks 0, 4, 12, and 24 after induction of adalimumab in 33 patients with Crohn's disease. Disease activity was determined by the Harvey-Bradshaw Index, ileocolonoscopy reports, cross-sectional imaging, C-reactive protein (CRP), and fecal calprotectin (FC) levels. Clinical remission was defined as Harvey-Bradshaw Index <5. Biological remission was defined as a combination of FC < 200 μg/g and CRP <5 μg/mL. ADL trough levels were tested using a liquid phase, mobility shift assay.**

RESULTS: **At 24 weeks, 18/33 (55%) of the patients were with biological remission. Ten (30%) patients required dose escalation or withdrawal from adalimumab by week 24 because of lack of response and exhibited significantly higher FC ($P = 0.003$) and CRP ($P = 0.002$). ADL levels at week 4 (19.8 μg/mL vs 10.2 μg/mL, $P = 0.001$) were significantly higher in patients with biological remission vs nonresponders at week 24. ADL levels at week 4 were a good predictor of biological remission at week 24, with area under the curve 0.86, 95% confidence interval (1.1; 1.67) and for combined biological and clinical remission, with area under the curve 0.8. The best ADL cutoff at week 4 that predicted biological remission at week 24 was 13.9 μg/mL (sensitivity 94.4% and specificity 73.3%).**

DISCUSSION: **In individuals with Crohn's disease, higher adalimumab drug levels at week 4 (>13.9 μg/mL) were significantly associated with biological remission at week 24.**

INTRODUCTION

Anti–tumor necrosis factor (TNF) agents have been established as effective treatment of Crohn's disease (CD) (1). In adults with moderately to severely active CD, adalimumab has demonstrated safety and improved disease outcomes (2,3). Early initiation of adalimumab after diagnosis has been shown to yield increased remission rates (4). However, despite the dramatic improvements in disease control and quality of life for responders to anti-TNF, a substantial proportion of adults with CD experience suboptimal response or no response (5). This is consistent with US health insurance claims data that reported initiation of a second-line therapy during a 24-month follow-up for 70% of individuals with CD who initiated an anti-TNF therapy (mostly adalimumab) (6). Moreover, up to 30% of adults who switch to a second biologic

because of lack of response or adverse events with the first biologic show suboptimal response making optimization of a first biologic important (7–9).

Higher serum concentrations of anti-TNF agents and undetectable antibodies have been shown to be associated with mucosal healing and other improved therapeutic outcomes in individuals with inflammatory bowel disease (IBD) (10–13). This has led to therapeutic drug monitoring (TDM), by which serum levels of biologics and antidrug antibodies are considered in dose adjustments. Reactive TDM entails adjusting drug dosing of patients who are nonresponsive to treatment. Proactive TDM aims to optimize the treatment of individuals with CD who presently respond favorably to treatment. The most recent clinical guidelines of the American Gastroenterology Association, published in

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2017 (14), issued a conditional recommendation regarding reactive TDM for adults with IBD treated with anti-TNF agents; this was by reason of the very low quality of evidence available. Because of a knowledge gap, the guidelines provide no recommendation regarding proactive monitoring in adults with quiescent IBD. By contrast, the Australian consensus statement on TDM for IBD, published in the same year, recommended proactive monitoring in certain circumstances (15). Furthermore, in December 2017, a panel of 13 international IBD specialists agreed that TDM of anti-TNF agents has therapeutic benefits and that drug concentrations of adalimumab drug levels (ADL) greater than 7 mg/mL are associated with an increased likelihood of mucosal healing (16). Notably, the current evidence for the benefit of proactive TDM is based mostly on retrospective studies and mostly on treatment with infliximab (IFX) rather than adalimumab (17–22). Although retrospective studies provide real-life data, the timing of the drug concentration assessment is generally variable. Moreover, the value of postinduction ADL at week 4 in predicting later disease remission is unclear.

We conducted a prospective, observational study to examine whether early ADL at week 4 predicted clinical and biological remission at week 24.

METHODS

Study design

This prospective observational study followed persons with CD for 24 weeks, from the initiation of adalimumab treatment who had a standard induction regimen, 160, 80, and 40 mg, every other week. All clinical examinations and assessments were performed according to the standard of care at our institution. ADL and adalimumab antibody (ATA) levels were measured at 4, 12, and 24 weeks after induction. Accordingly, study participants underwent physical and clinical assessments, as detailed below at 0, 4, 12, and 24 weeks after induction therapy with adalimumab.

Data collection and eligibility criteria

Adult patients aged 18–75 years diagnosed with active, moderate-to-severe luminal CD who were candidates for adalimumab induction therapy were eligible for this prospective longitudinal study. Baseline moderate-to-severe disease activity was defined by a simple endoscopic score-CD (SES-CD) >7, FC > 300 µg/g, and Harvey-Bradshaw Index (HBI) ≥ 5 and C-reactive protein (CRP) ≥5 µg/mL. All persons who met the inclusion criteria and attended the IBD program at Mount Sinai Hospital, Toronto, Canada, were identified and invited to participate in this study. Demographic and clinical information was obtained through chart review and patient interviews. Study exclusion criteria were cancer, acute or chronic enteric infection (e.g. *Clostridium difficile*), ulcerative colitis, current treatment with nonsteroidal anti-inflammatory drugs, dominant fibrostenotic disease with obstructive symptoms, surgery within 3 months of drug level collection, and the absence of a documented ileocolonoscopy or cross-sectional imaging study.

The study was approved by the institutional Research Ethics Board of Mount Sinai Hospital. All participants provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee (Research Ethics Board number 11-0108-C).

Outcomes

The primary endpoint was biological remission at week 24, defined by a combination of FC < 200 µg/g and CRP <5 µg/mL. The secondary endpoint was combined biological and clinical remission at week 24, defined by a combination of FC < 200 µg/g and CRP < 5 µg/mL and HBI < 4.

Measures and definitions

Serum adalimumab drug levels, ADL and ATA were measured 1–2 days before the drug administration date, at 0, 4, 12, and 24 weeks. Postinduction adalimumab drug level defined as ADL at week 4, 1–2 days before the drug administration. Measurements of serum trough ADL (µg/mL) and ATA (U/mL) were assessed using a liquid phase, mobility shift assay (Prometheus Laboratories, San Diego) (23). This is a drug-tolerant assay. ATA ≤ 1 U/mL was considered low titer. HBI and CRP were also measured at 0, 4, 12, and 24 weeks after induction.

Disease location was defined by the Montreal classification: small intestine CD (L_1), colonic CD (L_2), and ileocolonic CD (L_3), with or without upper gastrointestinal involvement (L_4) (24). An SES-CD 7–16 was defined as moderate clinical activity and a score >17 as severe activity (24). An HBI score of 8–16 was defined as moderate clinical activity and a score ≥17 as severe activity (25–27).

Fecal calprotectin (FC; µg/g) was collected within 1 week before preparation for colonoscopy and within 1 week before any further clinical visit study. FC was measured in our hospital laboratory kit, in a fresh stool samples by Buhlmann Quantum Blue Calprotectin High Range immunoassay (100–1800 µg/g) (28,29).

Statistical analysis

To compare the difference between patients' characteristics in both groups, the nonparametric Mann-Whitney U test was used for continuous variables, and the χ^2 test or Fisher exact test (when the assumption of the parametric χ^2 test was not met) was used to compare the categorical variables. The logistic regression analysis was performed for predicting for biological remission (defined by a combination of FC < 200 µg/g and CRP < 5 µg/mL) and combined measure of biological (defined by a combination of FC < 200 µg/g and CRP < 5 µg/mL) and clinical remission (defined as HBI < 5) at week 24 based on the ADL levels at week 4. The model-based odds ratio (OR) and its corresponding 95% confidence interval (CI) were calculated. We computed the 2-tailed P values, where $P < 0.05$ was considered a statistically significant result. A nonparametric receiver operating characteristic analysis using the DeLong method for calculating SEs was used to determine the capacity of ADL levels at week 4 to predict remission at week 24. Statistical analyses were performed using R statistical software version 3.6.1 (30).

RESULTS

Baseline characteristics

Thirty-three participants (n = 33) completed the prospective multivisit study (Table 1). The median age was 36 years (interquartile range 16), and 18 (55%) were men. At study entry, 19 (58%) were receiving concomitant immunomodulator therapy with either methotrexate or azathioprine. According to endoscopic scores, 25 were classified as having moderate SES-CD and 8 as severe SES-CD. According to HBI, 30 were classified as

Table 1. General clinical characteristics comparison of biological remission vs nonbiological remission at wk 24

Characteristic	All (n = 33)	Nonbiological remission (n = 15)	Biological remission (n = 18)	P value
Age, yr, median (IQR)	36.0 (16.0)	34.0 (9.0)	41.5 (17.0)	0.169
Sex, male, n (%)	18 (54.5)	11 (73.3)	7 (38.9)	0.048
Disease duration (y), median (IQR)	9.7 (12.0)	8.5 (9.9)	12.3 (16.5)	0.311
Smoking, n (%)	8 (24.2)	4 (26.7)	4 (22.2)	0.999
Albumin, median (IQR)	37.5 (34, 41)	37 (34, 40)	38 (35, 41)	0.666
Body mass index, median (IQR)	24.3 (23.1, 26.9)	24.2 (23.1, 26.4)	24.4 (23.3, 26.9)	0.889
Exposure to infliximab, n (%)	14 (42.4)	5 (33.3)	9 (50.0)	0.335
Disease location, n (%) (Montreal classification)				0.908
L1	10 (30.3)	4 (26.7)	6 (33.3)	
L2	14 (42.4)	7 (46.7)	7 (38.9)	
L3	9 (27.3)	4 (26.7)	5 (27.8)	
Concomitant therapy, n (%)	19 (57.6)	8 (53.3)	11 (61.1)	0.653
Endoscopic score, n (%)				0.700
Moderate activity—SES-CD 7-16	25 (75.7)	11 (73.3)	14 (77.7)	
Severe activity—SES-CD ≥17	8 (24.3)	4 (26.7)	4 (22.3)	
Clinical status, n (%)				0.7
HBI (%) moderate activity 8–16	30 (90.9)	13 (86.7)	17 (94.4)	
HBI (%) severe activity >16	3 (9.1)	2 (13.3)	1 (5.5)	
CRP, median (IQR)	13.1 (22.2)	18.8 (18.1)	7.2 (26.2)	0.247
Fecal calprotectin, median (IQR)	842.0 (984.0)	1,114 (851.0)	584.5 (808.0)	0.035

CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; IQR, interquartile range; SES-CD, simple endoscopic score for Crohn's disease.

having moderate disease activity and 3 as having severe clinical activity.

At 24 weeks after induction, 18 (55%) participants had FC < 200 μg/g and 24 had CRP < 5 μg/mL. The 18 participants who met both these criteria were considered to have achieved biological remission (FC < 200 μg/g and CRP < 5 μg/mL). Compared with participants who did not achieve biological remission, those who achieved biological remission at 24 weeks were less often men (39% vs 73%, $P = 0.05$) and with a lower median FC value (584.5 vs 1,114, $P = 0.035$) at baseline; the median CRP value was also lower, although without statistical significance: 7.2 vs 18.8, $P = 0.2$. Statistically significant differences were not found between participants who did and did not achieve biological remission in age at study entry, age at diagnosis, disease duration, smoking habits, previous exposure to IFX, disease location, the use of concomitant immunotherapy, endoscopic score, and clinical status according to HBI (Table 1).

By week 24, 31.3% (10/33) of the participants had required either dose escalation or withdrawal because of nonresponse. Their FC and CRP levels were significantly higher than those who achieved biological remission ($P = 0.003$ and $P = 0.002$, respectively).

Postinduction adalimumab drug level at week 4 and biological outcome at week 24

At week 4 after induction, 5 (15%) of the participants had detectable ATA titers (>1 U/mL). Four (80%) of these did not

achieve biological remission at week 24. None of the participants with elevated ATA titers at 12 and 24 weeks after induction achieved biological remission at 24 weeks (Table 2). Compared with participants who did not achieve biological remission at week 24, those who achieved biological remission had significantly higher ADL levels at week 4, median 19.8 vs 10.2 mg/mL ($P < 0.001$) (Figure 1), as well as at weeks 12 and 24 (Table 2).

The median ADL level at week 4 among the 5 participants with elevated ATA titers was lower than among the patients without elevated ATA (10.2 vs 19.8, μg/mL, $P < 0.001$) (Table 2). All 5 patients with detectible ATA (>1 U/mL) at week 4 were had clinical and biological relapse at week 24. Moreover, 3/5 patients with detectible ATA (>1 U/mL) at week 4 were with no detectible ADL level at week 24.

Of the 18 participants with biological remission at 24 weeks, 13 (72%) also achieved clinical remission. Of the 5 who achieved biological remission but not clinical remission at 24 weeks, 3 had mild clinical activity (HBI 5–7). The ADL level at week 4 was not a predictor of clinical remission at week 24: (OR = 1.00, area under the curve = 0.45, 95% CI [0.92–1.08], $P = 0.91$).

Associations between adalimumab concentrations at weeks 12 and 24 and biological remission at week 24

Adalimumab at week 12 was significantly associated with biological remission (OR = 1.30, χ[1] = 8.26, $P = 0.004$), and combined measures of clinical and biological remission (OR = 1.11, χ[1] = 4.15, $P = 0.042$), but not related to clinical remission

INFLAMMATORY BOWEL DISEASE

Table 2. Primary outcomes comparison of biological remission vs nonbiological remission at wk 4, 12, and 24

Characteristic	All patients (n = 33)	Nonbiological remission (n = 15)	Biological remission (n = 18)	P value	Method
ATA (bin, >1 U/mL) at wk 4, n (%)	5 (15.2)	4 (26.7)	1 (5.6)	0.152	Fisher exact test
ATA (bin, >1 U/mL) at wk 12, n (%)	3 (9.1)	3 (20.0)	0 (0.0)	0.083	Fisher exact test
ATA (bin, >1 U/mL) at wk 24, n (%)	6 (18.2)	6 (40.0)	0 (0.0)	0.005	Fisher exact test
ADL (mg/mL) at wk 4, median (IQR)	18.1 (10.0)	10.2 (8.9)	19.8 (6.9)	<0.001	Mann-Whitney U
ADL (mg/mL) at wk 12, median (IQR)	12.0 (11.2)	6.2 (8.2)	18.0 (9.2)	<0.001	Mann-Whitney U
ADL (mg/mL) at wk 24, median (IQR)	14.0 (13.4)	5.9 (16.7)	18.3 (13.1)	0.002	Mann-Whitney U

ADL, adalimumab drug levels; ATA, adalimumab antibodies; IQR, interquartile range.

(OR = 0.97, $\chi[1]$ = 0.44, P = 0.505). In the same way, adalimumab at week 24 was significantly associated with biological remission (OR = 1.17, $\chi[1]$ = 7.25, P = 0.007), but not with clinical and biological remission (OR = 1.08, $\chi[1]$ = 3.87, P = 0.049), or clinical remission alone (OR = 0.98, $\chi[1]$ = 0.45, P = 0.500).

Predictive model of clinical and biological remission at week 24 based on week 4

In logistic regression analysis, ADL level at week 4 was not a good predictor of combined outcome of clinical and biological remission at week 24: (OR = 1.08, P = 0.11). However, ADL level at week 4 was a good predictor of biological remission at week 24: (OR = 1.35 95% CI [1.1–1.67], P = 0.005, area under the curve = 0.86, 95% CI [0.64–0.98]) (Figure 2). Moreover, ADL at week 4 continued to be a good predictor for biological remission even by controlling additional baseline variables such as sex, age, weight, smoking, concomitant therapy, FC, or albumin (OR = 1.41, $\chi[1]$ = 7.84, P = 0.005) (Table 3): sex (OR = 1.92, $\chi[1]$ = 1.56, P = 0.21), age (OR = 1.07, $\chi[1]$ = 1.16, P = 0.28), weight (OR = 1.08, $\chi[1]$ = 1.63, P = 0.20), smoking (OR = 0.17, $\chi[1]$ = 1.67, P = 0.20), concomitant therapy (OR = 1.46, $\chi[1]$ = 1.17, P = 0.28),

FC (OR = 1.00, $\chi[1]$ = 1.60, P = 0.21), and albumin (OR = 1.33, $\chi[1]$ = 2.83, P = 0.09). Quartile analysis of ADL levels at week 4 also indicated strongest association with biological remission at week 24. In the lower quartiles, less than Q50 ADL at week 4, 33.33% of the patients were with no biological remission at week 24, and 18.18% were with biological remission at week 24. By contrast, in the higher quartiles, more then Q50 ADL at week 4, 12.12% of the patients were with no biological remission at week 24, and 36.36% of the patients were with biological remission at week 24 (Figure 3).

Optimal concentration at week 4 to reach biological remission at week 24

A nonparametric receiver operating characteristic analysis using the DeLong method for calculating SEs was applied to determine the optimal concentration ADL cutoff at week 4 value, which best discriminates subjects with biological remission from those without biological remission at week 24. The adalimumab drug level cutoff at week 4 that best predicted biological remission at week 24 was 13.9 µg/mL (sensitivity 94.4% and specificity 73.3%) (Figure 4). The adalimumab drug level cutoff at week 4 that best predicted integrative outcome of biological remission and clinical

Figure 1. ADL drug level at week 4 and biological remission at week 24. The median ADL trough levels at week 4 were significantly higher in the biological remission group compared with the nonbiological remission group at week 24 (19.8 vs 10.2 µg/mL, P = 0.001). ADL, adalimumab drug levels.
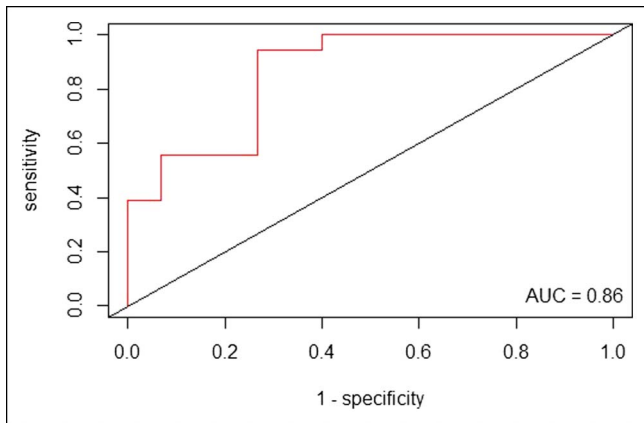
Figure 2. ADL levels at week 4 predicted biological remission at week 24, with (AUC = 0.86, 95% confidence interval [1.09; 1.67], sensitivity 94.4% and specificity 73.3%). ADL, adalimumab drug levels; AUC, area under the curve.

remission at week 24 was 16.2 μg/mL (92% sensitivity and 67% specificity).

DISCUSSION

We conducted a prospective study of individuals with moderately to severely active CD. We report the association of a higher ADL trough concentration at 4 weeks after induction with biological remission at 24 weeks, but not with combined outcome of clinical and biological remission, FC < 200 and CRP < 5 at week 24 or clinical remission alone at 24 weeks. An ADL level >13.9 μg/mL at 4 weeks was found to have the best sensitivity and specificity for predicting biological remission. Moreover, an ADL level >16.2 μg/mL at 4 weeks was found to have the best sensitivity and specificity for predicting combined biological remission and clinical remission at 24 weeks.

For most studies on TDM, the study design was retrospective and with outcomes based on clinical rather than objective biological data. Our results, using a prospective approach and with assessment of biological endpoints, provide information that is not evident from clinical data alone. Our finding of a lack of association of ADL trough levels with clinical remission is consistent with the recently reported findings of a Brazilian study, albeit on IFX in CD (31). In that study, drug trough levels did not

differ between individuals with active CD and those with CD in remission. This contrasts with the report by a longitudinal prospective study of an association between trough levels and clinical remission (32). However, that prospective study assessed trough levels at the end of induction, which was 10–12 weeks after induction, and not at 4 weeks' induction as in the current study. Moreover, the median ADL level at week 4 among the 5/6 participants with elevated ATA titers was lower than among the patients without elevated ATA (10.2 vs 19.8, μg/ML, P < 0.001), which supports the benefit of a drug-tolerant assay. A drug-sensitive assay would have suggested that the levels were in the suggested therapeutic range, but they also had antibodies at week 4 which ultimately led to zero of these patients achieving remission at week 24 (9).

The sample size of the current study was not large enough to ascertain a statistically significant association of ATA titers with biological remission. Nonetheless, elevated ATA titers were detected in 1 of 18 (6%) participants with biological remission and 4/15 (27%) without biological remission at 24 weeks. Other studies have demonstrated associations undetectable levels of antibodies with better clinical status in individuals with CD (9,33,34). Furthermore, the demonstration of an association between ATA titers and a lower ADL also concurs with other studies (9,27). Notably, in a cohort of 108 individuals with CD, trough levels of IFX associated more strongly with remission (11).

Nine (64%) of the participants with previous exposure to IFX achieved biological remission. This was not significantly different from the biological remission of 55% for the whole cohort. Notably, larger cohorts have demonstrated the effectiveness of adalimumab after IFX exposure. Accordingly, a multicentered randomized controlled trial of individuals with CD previously treated with IFX showed remission at 4 weeks after induction in 21% of those who received adalimumab compared with 7% who received a placebo (35). Moreover, a systematic review and meta-analysis demonstrated that therapies such as methotrexate or azathioprine, together with adalimumab, can yield effective results. The lack of association of concomitant therapy with biological remission concurs with a number of studies that reported no improvement in clinical remission among individuals with CD treated with adalimumab who received concomitant immunosuppressant therapy compared with adalimumab monotherapy (9,13,36). Notwithstanding this, given the rate of early antibody formation in this study and in the study by Kennedy et al. (5) (PANTS study), combination therapy with immune suppressants should be considered.

The question arises as to a maximum adalimumab dosage for safety and efficacy. Among adults with IBD in remission, higher anti-TNF serum concentrations were found to be associated with lower disease-specific quality of life; however, skin lesions and arthralgia were not more common (37). Elsewhere, adalimumab dose escalation to 80 mg every other week, shortening interval to 40 mg every week, demonstrated efficacy and safety in individuals with CD who lost response to maintenance adalimumab 40 mg every other week (38,39).

Strengths of this study include its prospective longitudinal design, which enabled TDM, adalimumab, and ADL at week 4 (after induction) in all participants by using an objective measurements outcome, such as CRP, FC, and ADL, in addition to subjective outcome such as HBI at week 24. Importantly, we evaluated whether higher ADL level at week 4 is a good predictor for better outcome at week 24 using an objective measurement

Table 3. Logistic regression ADL at wk 4 for biological and combined remission at wk 24

Predictors	Biological remission			Clinical and biological remission		
	B	CI	P	B	CI	P
Intercept	4.68	8.26 to −1.12	0.01	−1.75	−3.34 to 0.03	0.05
ADL (mg/mL) at wk 4	0.30	0.09 to 0.51	0.005	0.08	−0.02 to 0.17	0.11
Observations		33			33	
Tjur's R^2		0.446			0.122	

ADL, adalimumab drug levels; CI, confidence interval.
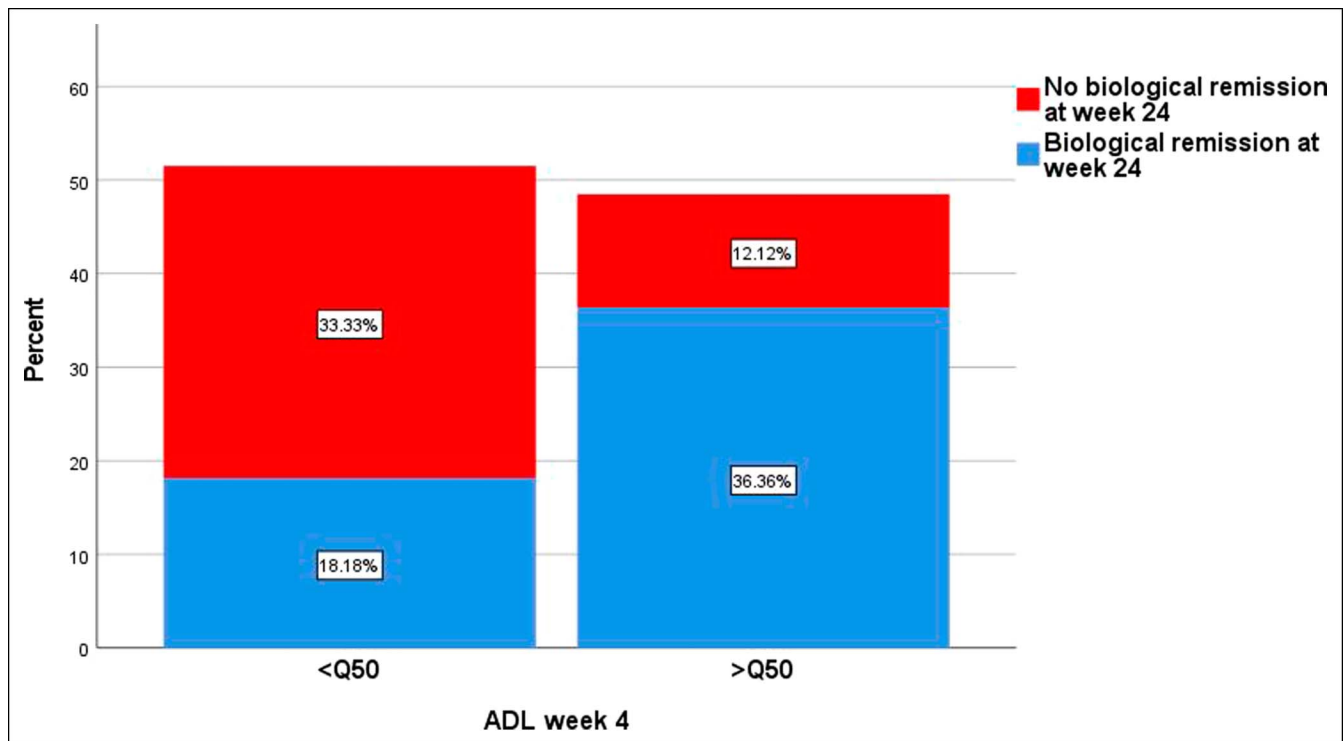
Figure 3. Quartile interval analysis of ADL levels at week 4 indicated a strongest association with biological remission at week 24.

rather than subjective measurements as used in previous studies. In previous studies, a substantial proportion of patients in symptomatic remission have been reported to demonstrate evidence of active disease, with elevated FC and CRP as a hallmark
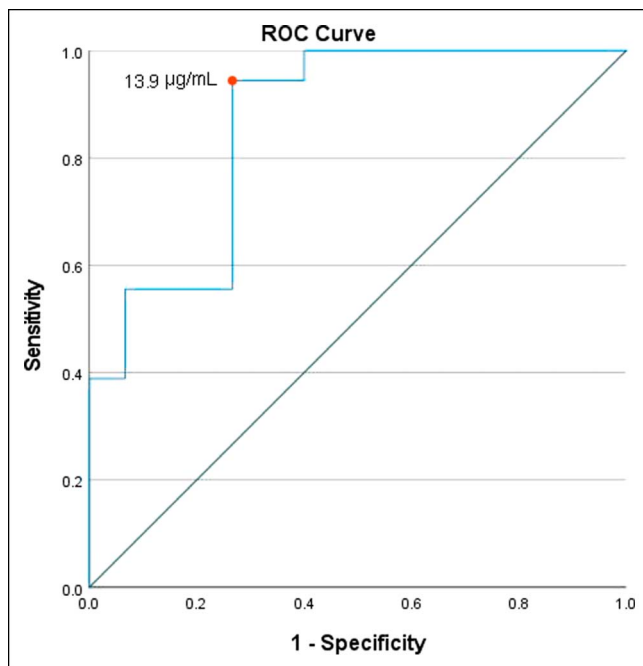
Figure 4. The ADL drug level cut-off at week 4 that best predicted biological remission at week 24 was 13.9 µg/mL (sensitivity 94.4%, specificity 73.3%).

for mucosal inflammation (40). Active mucosal inflammation and elevated CRP and FC have been shown to be good predictors of clinical relapse, disease progression, and complications in patients with IBD. In the effect of tight-control management on Crohn's disease (CALM) study, Colombel et al. used FC and CRP as surrogate biomarkers, biological remission, for mucosal activity, and as a noninvasive tool for a proactive approach with TDM (41). An additional strength of our study is the homogeneity of the cohort. This is due to the inclusion of patients with inflammatory CD only. A limitation of the current study is that the cohort was too small for statistical analysis of the association of ATA with the outcomes.

We believe that treatment regimens for patients with CD can be optimized with an active approach or tight-control scenario rather than a passive wait and see approach that lead to the major reason bad outcome and secondary loss of response to biologic treatment (42). A tight-control scenario is an algorithmic treatment pathway whereby physicians may modify treatment based on treat-to-target goals of patient-reported outcomes and/or laboratory data measured at predetermined intervals. For example, the CALM study was the first top-down study that compared remission rates of tight-control vs conventional clinical monitoring to escalate or deescalate biologic treatment (41).

TDM of adalimumab in patients with both low trough levels and low titers of antibodies benefits from dose optimization and combined immunosuppression (43,44). One study demonstrated that mucosal healing in patients with CD was strongly associated with higher trough concentration levels of adalimumab (median = 14.7 µg/mL) compared with nonmucosal healing patients who had lower trough levels (median = 3.4 µg/m; $P = 0.00006$) (10). The same study found the optimal adalimumab trough concentration cutoff for endoscopic mucosal healing to be 8.1 µg/mL,

which resulted in 91.4% sensitivity, 76.0% specificity, 84.2% positive predictive value, and 86.4% negative predictive value, suggesting that physicians can better manage patients with CD on adalimumab by targeting a specific trough level cutoff to better achieve mucosal healing.

A proactive approach to CD, TDM, and management through tight control in general as shown in our study might improve patient outcomes because it arms the physician with objective clinical data to make better informed therapeutic decisions, as demonstrated in all recent prospective trials.

Our findings corroborate a growing consensus of the effectiveness of proactive TDM with anti-TNF agents in IBD (22). The main contribution to the current literature is the demonstration of an association of early, 4-week, postinduction drug levels with later relevant biological variables. The ADL trough level at 4 weeks' induction was associated with the combined outcome of biological remission and clinical remission, yet not with clinical remission considered alone. An ADL level >13.9 μg/mL at 4 weeks was found to have the best sensitivity and specificity for predicting biological remission alone. Furthermore, higher ADL levels at week 4 were identified as the best predictor to reach clinical remission and biological remission at week 24. A cutoff of 16.2 μg/mL at week 4 best predicted biological remission at week 24, with 92% sensitivity and 67% specificity. This supports the importance of considering biological data and a proactive approach. Larger studies with longer follow-up are needed to ascertain the maintenance of biological remission and the subsequent clinical implications.

In summary, we found that higher ADL trough levels at week 4 were significantly associated with biological remission and biochemical remission alone at week 24. Moreover, higher ADL trough levels at week 4 were significantly associated with clinical remission and biological remission at week 24. The cutoff ADL trough level of 13.9 μg/mL demonstrated higher likelihood of achieving biological remission. The cutoff ADL trough level of 16.2 μg/mL demonstrated higher likelihood of achieving clinical remission and biological remission. We believe that these findings may contribute to therapeutic decision-making. Specifically, they highlight the patients who are more likely to achieve clinical remission and biological remission in week 24 can be identified by their ADL levels after induction phase in week 4. Further prospective long-term studies are needed to replicate our findings and to elucidate how a proactive approach based on therapeutic drug levels may facilitate achieving treatment goals in patients with CD.

Study Highlights

WHAT IS KNOWN

✓ A substantial proportion of adults with CD experience suboptimal response or no response Adalimumab (ADL).

✓ Most studies on therapeutic drug monitoring (TDM) outcomes were based on subjective clinical outcome rather than objective biological data.

WHAT IS NEW HERE

✓ We found in this prospective multi-visit study that higher Adalimumab (ADL) trough levels at week 4 were significantly associated with biological remission, combination of FC <200 μg/g and CRP <5 μg/mL, alone at week 24.

✓ In individuals with CD, higher adalimumab drug levels at week 4 (>13.9 μg/mL) were significantly associated with biological remission at week 24.

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