

Therapeutic drug monitoring of ustekinumab in Crohn's disease patients: a real-world study

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Abstract

Crohn's disease (CD) is a chronic inflammatory disorder. Ustekinumab (UST) is an effective treatment for CD. Therapeutic drug monitoring (TDM) enhances clinical efficacy while minimizing side effects. This study aimed to evaluate the UST trough level (TL) and anti-drug antibodies (ADAs) and to assess the response of patients with CD to optimize UST treatment. This single-center, cross-sectional study included 76 adult patients with CD receiving maintenance UST for at least 24 weeks. The serum TL of UST and clinical remission were assessed at the same visit, immediately before the next dose. Patients were categorized into two groups: Group A, patients reaching the UST target TL ($\geq 1 \mu\text{g/mL}$), and Group B, patients failing to reach it. The association between UST exposure and remission was assessed by binary logistic regression. The remission rate was significantly higher in Group A (78.2%) than in Group B (28.6%) ($p < 0.001$). Based on the TL of UST, ADA positivity, and disease activity, recommendations were made to continue treatment in 43 patients, escalate therapy or shorten the dosing interval in 20 patients, and switch to another biologic agent in 13 patients. Accordingly, TDM of UST could serve as a valuable approach for optimizing CD therapy.

Keywords

Anti-drug antibody, Crohn's disease, therapeutic drug monitoring, trough level, ustekinumab

Introduction

Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is a long-lasting inflammatory condition that can affect any part of the gastrointestinal system (Bon 2025). A recent meta-analysis of 215 population-based studies estimated the global pooled prevalence of CD at 84.2 per 100,000 (Heydari et al. 2025). The average age at the onset of CD is 30 years, with two peaks: the first between 20 and 30 years and a smaller peak near 50 years (Feuerstein and Cheifetz 2017).

The onset of CD is believed to stem from the intricate interplay of genetic predisposition, environmental

influences, and gut microbiota. This interaction may result in an irregular mucosal immune reaction and compromised epithelial barrier function (An et al. 2026).

The management of CD has improved due to an enhanced understanding of the immune mechanisms related to the pathogenesis of the disease. This understanding has resulted in the development of various biological treatments, such as monoclonal antibodies that specifically inhibit crucial inflammatory mediators, including tumor necrosis factor (TNF). Infliximab and adalimumab were introduced first, followed by other biologics with distinct mechanisms of action for managing CD in practice. Vedolizumab acts as a gut-selective blocker of

$\alpha 4\beta 7$ integrin, while ustekinumab (UST) is a human IgG1 monoclonal antibody targeting the p40 subunit common to IL-12 and IL-23. UST effectively induces and maintains remission in patients with IBD resistant to anti-TNF therapies or standard treatments. Moreover, UST showed efficacy in perianal refractory CD and various extraintestinal manifestations (Macaluso et al. 2023; Zhang et al. 2024).

Although biologics are successful in managing IBD, as many as 30% of patients are primary non-responders, and an additional 50% experience secondary loss of response (SLR) over time (Cheifetz et al. 2021). Three primary failure mechanisms in biologic treatment have been suggested. The initial type is “non-immune-mediated pharmacokinetic failure,” associated with the drug’s swift elimination. The second mechanism involves “immune-mediated pharmacokinetic failure” due to the generation of neutralizing anti-drug antibodies (ADAs) targeting biologics, which manifests as a secondary loss of response during the biologic therapy maintenance phase. The third mechanism is “mechanistic failure,” where IBD might be driven by inflammatory processes that are not inhibited by the administered biologics (Al-Jalehawi and Mohammed 2024; Mansur Kadhim et al. 2026). The clearance of UST may be affected by factors such as body weight, serum albumin levels, immunogenicity, prior use of biologics, male sex, Asian ethnicity, and elevated C-reactive protein (CRP) (Geoffrey Metz 2024).

Therapeutic drug monitoring (TDM) has become an essential method for personalized dosing, mainly because of the identified link between serum drug levels and treatment results. Accordingly, assessing drug concentrations and ADAs will support therapeutic strategies and can assist physicians in deciding whether to adjust therapy within or outside a specific class (Alsoud et al. 2020).

TDM can take two forms: reactive TDM, which involves the evaluation of drug concentrations in patients with primary non-response or SLR to a biologic (Shubow et al. 2025), where measurements are taken in response to active disease (Dutt and Vasudevan 2024). Conversely, proactive TDM routinely evaluates drug concentrations at predetermined points in time during quiescent disease or clinical remission to ensure that drug levels are achieved and maintained (Wu 2022).

Serum UST concentration is not regularly checked in clinical settings, and there is scant evidence for therapeutic drug monitoring with this treatment. Existing information regarding the relationship between trough serum UST drug levels and clinical outcomes in IBD is inconsistent, rendering the role of TDM more ambiguous (Dutt and Vasudevan 2024).

A 2021 meta-analysis recommended target UST trough levels of 1–3 $\mu\text{g/mL}$ during the maintenance treatment phase and suggested a cut-off of approximately 1 $\mu\text{g/mL}$ of UST concentration for forecasting clinical remission (Restellini and Afif 2021).

This study aimed to measure the TL of UST and ADA concentrations and evaluate the response of Iraqi patients with moderate-to-severe CD to provide suitable suggestions for adjusting UST therapy. The other aim was to study the possible association between different factors

(sociodemographic factors, disease characteristics, and inflammatory markers) and the achievement of the target serum UST concentration.

Patients, materials, and methods

Study design and setting

A cross-sectional study was carried out from January to June 2026 at the Gastroenterology and Hepatology Teaching Hospital/Medical City/Baghdad/Iraq, which is considered a center for treating patients with CD from all Iraqi governorates, from north to south. The current study used a convenience sampling method. All eligible adult patients with CD receiving maintenance UST therapy who attended the center during the study period (January–June 2026) and met the inclusion criteria were enrolled.

The study enrolled 76 patients; each patient was monitored by a specialist gastroenterologist and was treated according to clinical protocols (Gordon et al. 2024). All patients received an induction dose intravenously based on body weight at week 0: 260 mg for less than 55 kg, 390 mg for 55–85 kg, and 520 mg for more than 85 kg, followed by a maintenance dose of 90 mg subcutaneously every 8 weeks, starting 8 weeks after the induction dose. All enrolled patients received maintenance UST every 8 weeks and had completed at least 24 weeks of continuous therapy before inclusion, ensuring sampling at pharmacokinetic steady state. Sampling was not linked to a specific numbered dose but was performed once a patient had exceeded 24 weeks of treatment. Each patient was sampled on a single occasion.

Detailed family, medical (chronic diseases, concomitant use of immunosuppressants, and previous biologic therapy), and smoking histories were collected. Clinical response was evaluated using the Crohn’s disease activity index (CDAI) score, where remission was defined as a CDAI score < 150; values ≥ 150 indicated active disease (Best et al. 1976).

Inclusion and exclusion criteria

Patients were eligible for inclusion if they were 18 years or older, had documented CD, and agreed to participate in the study. In addition, eligible patients were required to receive maintenance UST therapy, defined as receiving an induction dose and at least two subcutaneous maintenance doses of UST for a minimum total treatment duration of 24 weeks.

Patients were excluded if they declined to participate in this study. Patients were also excluded if they had other immune system conditions (such as rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and systemic lupus erythematosus), as these conditions provide a strong rationale for corticosteroid use that could influence serum biomarker concentrations, or if they had received systemic or rectal steroids in the last 3 weeks. In addition, patients were excluded if they had known cancer or a previous history of cancer or were experiencing complications from CD that may necessitate surgery or could complicate the evaluation of UST treatment effects via the CDAI,

including active stoma, short-gut syndrome, and severe or symptomatic strictures or stenosis. Patients with insufficient monitoring data were also excluded from the study.

Study groups

Patients were divided into two groups (Restellini and Afif 2021):

Group A: Patients who met the UST target TL (≥ 1 $\mu\text{g/L}$).

Group B: Patients who failed to reach the UST target TL (< 1 $\mu\text{g/mL}$).

Study parameters and outcomes

Clinical assessment

Crohn's Disease Activity Index (Best et al. 1976): Clinical disease activity was assessed using the CDAI score at the same study visit at which a blood sample to measure UST TL was obtained so that TL and disease activity represented the same time point for each patient. Because all patients had completed at least 24 weeks of continuous UST therapy before inclusion, CDAI was therefore assessed after a minimum of 24 weeks from initiation of UST, during maintenance treatment. Clinical remission was defined as CDAI < 150 .

Laboratory assessment

All laboratory parameters and inflammatory biomarkers were measured from the same single blood sample obtained at the same study visit as the UST TL and CDAI assessment and therefore at a minimum of 24 weeks of UST therapy during maintenance treatment. These included UST TL, measured using a quantitative ELISA kit based on indirect enzyme-linked immunosorbent assay technology (Catalogue No. EH5320, Fine Test); anti-drug antibody, measured using a qualitative enzyme-linked immunosorbent assay (ELISA) kit based on sandwich enzyme-linked immunosorbent assay technology (Catalogue No. EH5321, Fine Test); and routine laboratory tests, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), and serum albumin level. CBC was estimated using Sysmex XP-300 hematology analyzers (Sysmex, Germany), which are 3PD (3-part differential) analyzers that use a DC (direct current) detection method. For ESR, the test was performed using the Mixrate X20 ESR Auto-analyzer from Vital Diagnostic, Italy. C-reactive protein (CRP) was measured using the Cobas c 111 analyzer from Roche, Switzerland, with a latex-enhanced immunoturbidimetric assay that uses latex spheres as markers in an immunological technique based on antigen-antibody reactions.

Blood sample collection and storage

Approximately 10 mL of venous blood was collected to measure the TL of UST and other parameters at the end of the 8-week dosing interval, on the same day as the next

scheduled maintenance dose and immediately before its administration (within a few minutes). Patients required no fasting, and no specific preparation was required before sampling. Blood samples were collected in three separate tubes: an EDTA tube (to measure CBC), a gel tube (for TDM), and a black-top tube (for ESR). Centrifugation at 4,000 rpm for 10 min was performed to separate the serum, and the serum was then transferred into labeled Eppendorf tubes. Serum samples were stored at -80 °C until analysis; all samples were analyzed within 5 months of collection.

Ethical approval

The Scientific and Ethical Committee of the College of Pharmacy, University of Baghdad (approval number: RE-CAUBCP179202575H; date: 17 September 2025), along with the Iraqi Ministry of Health, approved this study. Consent was obtained from all participants. Participation was completely optional, and no rewards were provided.

Statistical analysis

The Shapiro–Wilk test was employed to assess the normality of the study variables. Variables that followed a normal distribution were expressed as mean $\pm$ standard deviation, while those that did not were expressed as median (interquartile range). Categorical variables were displayed as frequencies and proportions (n , %). An independent t -test was applied to assess normally distributed variables, while the Mann–Whitney U test was utilized for non-normally distributed data. The chi-square test was utilized for categorical variables. To quantify the association between UST exposure and clinical remission, binary logistic regression was performed with UST TL as a continuous predictor (per 1 $\mu\text{g/mL}$) and clinical remission (CDAI < 150) as the binary dependent variable. Effect estimates were expressed as odds ratios (OR) with 95% confidence intervals (CI) and two-tailed p -values. A multivariate binary logistic regression was performed to determine whether the association between UST TL and clinical remission persisted after adjusting for potential confounders. The number of covariates in the multivariate analysis was constrained by the events-per-variable (EPV) principle (27 patients with active disease) to avoid overfitting and unstable estimates. Data analysis was performed using SPSS version 20 (IBM Corp., USA), with statistical significance defined as $P < 0.05$.

Results

The present study enrolled 76 patients with CD, and their demographic and disease characteristics are presented in Table 1. The median age of the participants was 30 years. Sex was approximately evenly distributed, with 52.6% females and 47.4% males. The average BMI of the participants was 24.37 ± 5.75 kg/m^2 . The median duration of CD

Table 1. Demographic and clinical data of the study population ($N = 76$).

Variables	Results
Age (years) [median, (IQR)]	30.00 (24.00–38.00)
Sex	
Male [n (%)]	36 (47.4%)
Female [n (%)]	40 (52.6%)
BMI (kg/m ²) [mean $\pm$ SD]	24.37 $\pm$ 5.75
Smoking [n (%)]	
-Current	18 (23.7%)
-Never	58 (76.3%)
Duration of the disease (years) [median, (IQR)]	5.50 [4.00–10.00]
Duration of UST treatment (months) [median, (IQR)]	12.00 (10.00–24.00)
Concomitant medications (immunosuppressant) [n (%)]	29 (38.2%)
History of using other biology	
Previous biology [n (%)]	71 (93.4%)
Naive-	5 (6.6%)
Family history of CD [n (%)]	11 (14.5%)
Comorbidities [n (%)]	5 (6.6%)
Response (according to CDAI score)	
-Remission [n (%)]	49 (64.5%)
-Active disease [n (%)]	27 (35.5%)

BMI: Body Mass Index, **CD:** Crohn's disease, **CDAI:** Crohn's Disease Activity Index, **IQR:** interquartile range, **SD:** standard deviation, **UST:** ustekinumab. Data are expressed as either mean $\pm$ SD for normally distributed numeric variables, as median (IQR) for non-normally distributed numeric variables, or as n (%) for categorical variables.

was 5.5 years, while the median duration of UST treatment was 12 months. The results of the patients' clinical history showed that, of the 76 patients, 71 (93%) were biologic-experienced, and five (6.6%) were biologic-naïve. All biologic-experienced patients had previously received both infliximab and adalimumab, representing prior exposure to two anti-TNF agents.

Of the participants, 23.7% were smokers, 14.5% had a family history of CD, 38.2% used immunosuppressants (azathioprine) with UST, and 6.6% had medical comorbidities, mostly diabetes mellitus or hypertension.

Table 2 shows a comparison between the study groups: Group A, who achieved the target TL, and Group B, who did not achieve it, in terms of demographic and disease-related variables. No significant differences were observed in sex distribution, smoking, BMI, disease duration, or UST duration ($p > 0.05$ for all comparisons). The median age was higher in Group B (36 years) than in Group A (29 years), but the difference was not statistically significant ($p = 0.085$). No significant differences were observed between the study groups in terms of family history of CD, having other comorbidities, history of using biologics other than UST, or concomitant use of immunosuppressants (azathioprine) ($p > 0.05$ for all comparisons). A highly significant difference was found in clinical remission between the two groups, with achievement of the target trough level being strongly associated with clinical remission ($p < 0.001$).

Table 2. Demographic and disease characteristic comparisons between Crohn's disease patients in Group A (achieved trough level) and Group B (did not achieve trough level).

Variables	Study groups		P-value
	Group A	Group B	
	(TL $\geq 1\mu\text{g/mL}$) N = 55	(TL < $1\mu\text{g/mL}$) N = 21	
Age (years) [median, (IQR)]	29.00 [24.00–35.00]	36.00 [25.00–48.00]	0.085 ^c
Sex			
Male [n (%)]	25 (45.5%)	11 (52.4%)	0.589 ^a
Female [n (%)]	30 (54.5%)	10 (47.6%)	
BMI (kg/m ²) [mean $\pm$ SD]	23.99 $\pm$ 4.31	25.38 $\pm$ 8.51	0.482 ^b
Smoking [n (%)]			
Current-	13 (23.6%)	5 (23.8%)	0.987 ^a
-Never	42 (76.4%)	16 (76.2%)	
Duration of the disease (years) [median, (IQR)]	6.00 [4.00–10.00]	5.00 [4.00–8.00]	0.700 ^c
Duration of UST treatment (months) [median, (IQR)]	12.00 [10.00–18.00]	24.00 [12.00–36.00]	0.081 ^c
Concomitant medications [n (%)]	24 (43.6%)	5 (23.8%)	0.112 ^a
History of using other biology [n (%)]			
-Previous biology	53 (96.4%)	18 (85.7%)	0.126 ^d
- Naive	2 (3.6%)	3 (14.3%)	
Family history of CD [n (%)]	9 (16.4%)	2 (9.5%)	0.717 ^d
Comorbidities [n (%)]	3 (5.5%)	2 (9.5%)	0.612 ^d
CDAI score	131 (85–147)	197 (127–273)	0.004 ^{c *}
Response (according to CDAI score)			
-Remission [n (%)]	43 (78.2%)	6 (28.6%)	< 0.001 ^{a *}
-Active disease [n (%)]	12 (21.8%)	15 (71.4%)	

BMI: Body Mass Index, **CD:** Crohn's disease, **CDAI:** Crohn's Disease Activity Index, **IQR:** interquartile range, **SD:** standard deviation, **UST:** ustekinumab. [a] Chi-square test; [b] independent two-sample t -test; [c] Mann–Whitney U test; [d] Fisher's exact test. [*] Significant differences [$p < 0.05$].

Table 3 presents a comparison of the TL and ADA positivity between the study groups. A highly significant difference in the median TL of UST was observed between the two groups, with higher drug concentrations observed in Group A ($p < 0.001$); on the other hand, no statistically significant difference in ADA positivity was observed between the study groups ($p = 0.276$).

Table 3. Comparisons between Crohn's disease patients in Group A and Group B based on UST TL and anti-drug antibody.

Variables	Group A N = 55	Group B N = 21	P-value
TL ($\mu\text{g/mL}$) [median (IQR)]	1.50 (1.25–1.73)	0.70 (0.56–0.87)	<0.001 ^{ck}
ADA positive [n (%)]	0 (0.0%)	1 (4.8%)	0.276 ^d

ADA: anti-drug antibody; TL: trough level. (c) Mann–Whitney *U* test; (d) Fisher's exact test; (*) significant difference ($p < 0.05$).

Table 4 presents the classification of patients with CD by TL of UST, ADA, and disease activity (remission and active disease by CDAI score), along with related recommendations. The recommendations involved UST dose escalation or dosage interval shortening for 20 patients, therapy continuation for 43 patients, and switching to an alternative therapy for 13 patients.

Table 4. Classification of patients and recommendations based on TL, ADA, and disease activity.

Patients who achieved the target TL ($n = 55$)			Patients who did NOT achieve the target TL ($n = 21$)	
(43 patients) with remission	(12 patients) with active disease	Six patients with remission	15 patients with active disease	
	Mechanistic treatment failure *		14 patients with negative ADA "Non-immune pharmacokinetic failure"	One patient with positive ADA "Immune pharmacokinetic failure" **
Recommendations				
Continue therapy	Switch therapy	Escalate therapy or shorten dose interval	Escalate therapy or shorten dose interval	Switch therapy

ADA: anti-drug antibody; TL: trough level. * Mechanistic treatment failure: active disease despite target drug levels without ADAs occurs when the disease (CD) might be driven by inflammatory processes that are not inhibited by the administered biologics. ** Immune pharmacokinetic failure: low drug levels driven by positive ADAs occur due to the generation of neutralizing anti-drug antibodies targeting biologics, which manifests as a secondary loss of response during the biologic therapy maintenance phase.

Table 5. Comparison of Crohn's disease patients in Group A and Group B based on various laboratory data and inflammatory biomarkers.

Variables	Study groups		P-value
	Group A N = 55	Group B N = 21	
WBCs ($10^9/\text{L}$) [median (IQR)]	7.90 (6.70–9.40)	7.80 (5.70–9.90)	0.754 ^c
Lymphocyte count ($10^3/\mu\text{L}$) [median (IQR)]	1.90 (1.60–2.50)	2.00 (1.20–2.60)	0.301 ^c
Neutrophil count ($10^3/\mu\text{L}$) [mean $\pm$ SD]	5.24 $\pm$ 1.87	5.31 $\pm$ 1.87	0.884 ^b
HGB (g/dL) [median (IQR)]	13.00 (12.00–14.20)	12.50 (10.75–13.60)	0.329 ^b
PCV (%) [mean $\pm$ SD]	39.23 $\pm$ 4.50	38.38 $\pm$ 4.65	0.471 ^c
PLT ($10^3/\mu\text{L}$) [median (IQR)]	293.00 (241.00–371.00)	360.00 (270.00–463.00)	0.093 ^c
Serum albumin (g/L) [median (IQR)]	41.60 (38.00–43.00)	35.00 (32.00–40.00)	< 0.001 ^{ck}
ESR (mm/hr) [median (IQR)]	24.00 (14.00–31.00)	64 (22.50–78.50)	< 0.001 ^{ck}
CRP (mg/L) [median (IQR)]	1.90 (0.60–10.00)	22.00 (7.35–35.10)	< 0.001 ^{ck}

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HGB: hemoglobin; IQR: interquartile range; PCV: packed cell volume; PLT: platelets; SD: standard deviation; WBCs: white blood cells. (b) Independent two-sample *t*-test; (c) Mann–Whitney *U* test. (*) Significant differences ($p < 0.05$).

Table 5 summarizes the laboratory data and inflammatory markers. No statistically significant differences were found between the two groups in white blood cell (WBC) count, lymphocyte count, neutrophil count, hemoglobin, or packed cell volume ($p > 0.05$ for all comparisons). The median platelet count was higher in Group B, but the difference was not statistically significant ($p = 0.093$). The median serum albumin level was significantly higher in Group A patients ($p < 0.001$); in this group of patients, inflammatory markers (ESR and CRP) were significantly lower than those in Group B ($p < 0.001$).

Table 6 quantifies the exposure–response relationship; binary logistic regression was performed with UST TL as a continuous predictor. Higher trough concentrations were significantly associated with clinical remission: each 1 $\mu\text{g/mL}$ increase was associated with an approximately nine-fold increase in the odds of remission (OR 9.35, 95% CI 2.61–33.33; $P = 0.001$).

Table 7 shows that higher UST TL remained independently associated with clinical remission after adjustment for potential confounders, including concomitant azathioprine use and UST treatment duration (adjusted OR 14.30, 95% CI 3.35–58.80; $P < 0.001$). Neither azathioprine use nor UST treatment duration was associated with clinical remission.

Table 6. Association between UST trough level and clinical remission by univariate analysis.

Variable	Univariate analysis	
	OR (95% CI)	P-value
TL (per 1 µg/mL)	9.35 (2.61–33.33)	0.001 e*

CI: confidence interval; OR: odds ratio; TL: trough level. (e) Binary logistic regression was used. (*) Significant difference ($p < 0.05$).

Table 7. Association between UST trough level and clinical remission by multivariate logistic regression, adjusted for covariates.

Variable	Multivariate analysis	
	Adjusted OR (95%CI)	P-value
UST TL (per 1 µg/mL)	14.3 (3.35–58.80)	<0.001* f
Concomitant immunomodulator use	2.11 (0.67–6.63)	0.199
UST treatment duration	0.97 (0.93–1.01)	0.165

CI: confidence interval; OR: odds ratio; TL: trough level; UST: ustekinumab. (f) Multivariable binary logistic regression was used. (*) Significant difference ($p < 0.05$).

Discussion

This study was conducted to evaluate the applicability of TDM in Iraqi patients with moderate-to-severe CD treated with UST. Based on a comprehensive literature review, this is the first clinical study in Iraq to assess the TL and ADA of UST in patients with CD.

The findings of the present study should be interpreted in the context of the study design and the timing of measurements; UST trough concentration and disease activity were assessed concurrently, with a single blood sample obtained at steady state after at least 24 weeks of maintenance therapy and immediately before the next scheduled dose, so that the exposure and outcome reflect the same time point for each patient.

As shown in Table 2, the patients were divided into Group A ($n = 55$) and Group B ($n = 21$) according to the achievement of the target TL. No statistically significant differences in age, sex, BMI, disease duration, history of smoking, family history of CD, use of concomitant medication, or previous biologic therapy were observed between the two groups ($p > 0.05$).

The CDAI scores were significantly higher in non-achievers (Group B) than in achievers (Group A) ($p = 0.004$); therefore, the remission rate in achievers was 43/55 (78.2%), compared with 6/21 (28.6%) in non-achievers, indicating that achievement of the target TL was highly associated with clinical remission. Previous studies showed conflicting results; some showed positive associations between TL and clinical response, such as a Spanish study that emphasized the existence of an association between the TL of UST and clinical response in a large real-world cohort including a significant proportion of patients with optimized UST regimens (González-Antuña et al. 2024). Another study from the Netherlands showed no association between UST levels and corticosteroid-free clinical remission rates (Straatmijer et al. 2023). An Italian study also showed that TLs did not correlate with clinical remission (Bertin et al. 2024).

From the results in Table 3, the median TL of UST was significantly higher in Group A (1.50 µg/mL) than in Group B (0.70 µg/mL) ($p < 0.001$). A multicenter study reported that a TL of UST of 0.8 (or even up to 1.4 µg/mL) or greater was associated with the maintenance of clinical remission in a higher proportion of patients than in patients with lower TLs (Adedokun et al. 2018). A recent systematic review and meta-analysis showed that the median TLs of UST were higher among individuals achieving clinical remission than among those not achieving remission (mean difference, 1.6 µg/mL) (Vasudevan et al. 2024). A Chinese multicenter retrospective and observational study showed that maintaining UST drug concentrations at or above 3.0 µg/mL was associated with sustained clinical remission and reduced disease relapse (Ren et al. 2025). The differences in the TL of UST associated with clinical remission among studies could be explained by different endpoints of clinical remission and endoscopic improvement. In addition, UST and ADA concentrations were measured using different laboratory assays (ELISA and drug-tolerant liquid-phase HMSA) (Restellini and Afif 2021). This may also be due to the measurement of drug concentrations during either the induction or maintenance phase, as well as differences in the UST dosing interval of every 8 or 12 weeks. In the current study, all patients received UST at an 8-week interval. No statistically significant difference was observed in ADA positivity between the two groups, with only one patient (1/21; 4.8%) being positive in the non-achiever group and experiencing relapse. The prevalence of patients positive for UST anti-drug antibodies ranged between 4.2% and 5.6% (Hanauer et al. 2020; Vasudevan et al. 2024), while the results of a study conducted on patients with psoriasis treated with UST demonstrated that only two patients (2.6%) tested positive in the non-achiever group, supporting the idea that immunogenicity may not have an impact on serum levels of UST (Yahya et al. 2025).

The categorization of patient samples (76 patients) according to TL, ADAs, and disease activity revealed significant information regarding the mechanisms that influence treatment success or failure in patients with CD (Table 4). In this research, 55 individuals (Group A) reached the target TL for UST (72.36%). Most of them (43/55) attained clinical remission, highlighting the significance of ensuring sufficient drug exposure for effective treatment. It is advised to continue treatment for these patients. Nonetheless, 12/55 of them showed active disease, signifying mechanistic treatment failure. Mechanistic failure occurs when the patient does not respond to suitable medication. Such a failure likely occurs when the specific medication does not inhibit inflammatory mediators that drive the disease process (Saleh et al. 2024b). The recommendation for these patients is to change the treatment rather than adjust the dosage (Shubow et al. 2025).

In 21 patients (27.63%), the target TL was not reached despite ongoing UST treatment (Group B). Only six of them showed clinical remission. These patients benefited from UST therapy despite low levels. The clinical recommendation for them is to escalate the UST dose or shorten the dosage interval (Shubow et al. 2025), such as

every 4 weeks instead of 8 weeks, to prevent future loss of response. Among patients with active disease, 14/21 had negative ADA, indicating non-immune pharmacokinetic failure, which may be due to patient-related factors, such as BMI, disease duration, and history of TNF inhibitor use, which are considered predictors of poor UST response (Xu et al. 2021). The recommendation for these patients is to escalate the UST dose or shorten the dosage interval to restore therapeutic drug levels, except for one patient (1/21) who had positive ADA. This patient experienced immune pharmacokinetic failure, and the recommendation is to switch to another biologic therapy with a different mechanism of action (Shubow et al. 2025).

Table 5 shows the results of laboratory findings and inflammatory markers; no statistically significant differences were observed between the two groups in terms of WBC count, neutrophil count, lymphocyte count, hemoglobin, packed cell volume, or platelet count.

Significant differences in serum albumin, ESR, and CRP levels were observed between the two groups. A recent American study showed that both ESR and CRP values were significantly lower in patients with IBD with adequate UST levels than in those with low UST levels (Saleh et al. 2024a). ESR and CRP are acute-phase proteins that increase in response to inflammation and various other conditions. Additionally, CRP might demonstrate greater sensitivity than ESR and show a stronger correlation with disease activity in IBD; while both CRP and ESR can occasionally be employed to monitor disease activity, normal values of ESR and CRP do not rule out IBD complications or disease flare-ups (Saleh et al. 2025). The inverse relationship between UST levels and CRP concentrations indicates that patients with the highest inflammatory load have quicker UST elimination. These patients might benefit from a reduced administration interval (Restellini and Afif 2021). A study on UST in patients with psoriasis found significantly higher hs-CRP levels in patients who did not respond optimally to UST; at the same time, ESR showed no significant differences between responders and non-responders (Yahya et al. 2026).

Serum albumin levels were significantly higher in achievers than in non-achievers, aligning with a Japanese study that found a significant positive correlation between UST trough levels and serum albumin levels (Morita et al. 2020).

Limitation

This study has certain limitations. First, it used a convenience sampling method for patients attending a single

center during a defined period of time; patients' availability therefore constrained the sample size. The relatively limited sample size may affect the statistical power and generalizability of the findings. In addition, enrolling patients from one center could introduce selection bias and restrict external validity. Ultimately, the assessment of TL and ADA was postponed because the patient samples were collected and preserved for approximately 5 months before laboratory evaluation. Consequently, the time gap between sampling and result availability resulted in the postponement of treatment advice for both clinicians and patients. More extensive, multicenter research is needed to confirm these results and enhance the understanding of the role of TDM in patients with CD undergoing UST treatment.

Conclusion

In conclusion, the results of the current study highlight the importance of TDM for patients with CD on UST and explain the possible causes of disease activity in some patients despite adherence to their treatment schedule. Higher UST trough concentrations were significantly and independently associated with clinical remission; patients who achieved the target trough concentration were more likely to achieve remission than those who did not. Adequate UST exposure was also associated with a significantly lower inflammatory burden (ESR and CRP) and higher serum albumin. Based on the TL of UST, ADA positivity, and disease activity, recommendations were made to continue treatment, escalate therapy, shorten the dosage interval, or switch to another biologic agent. This study's recommendations could guide clinicians in tailoring decisions for each patient and show the therapeutic benefits of integrating TL and ADA evaluation in practical applications.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: College of pharmacy- University of Baghdad

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.

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The contributions of the authors were as follows: the first and third authors collected data; the second author conceived and designed the study; the first and second authors prepared the draft manuscript; and all authors examined and approved the final version of the manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.