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Research Article

Therapeutic drug monitoring of adalimumab for dose optimization during maintenance therapy in patients with ulcerative colitis: real-world data

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Abstract

Introduction: Ulcerative colitis (UC) is a chronic inflammatory disease that primarily affects the colon. Tumor necrosis factor-α inhibitors (like adalimumab) are effective agents for UC. However, loss of response may occur. Proactive therapeutic drug monitoring involves measuring drug levels at regular intervals in patients in remission to maintain therapeutic concentrations and potentially prevent loss of response.

Aim: This study aims to evaluate adalimumab trough level (TL), the development of anti-drug antibodies (ADAs), and their relationships with clinical and laboratory variables in Iraqi patients with ulcerative colitis receiving adalimumab therapy.

Patients and methods: The present study was cross-sectional and conducted from April 2024 to November 2024. It included 44 UC patients allocated into 2 groups: group 1 (patients with TL within or above the therapeutic range) and group 2 (patients with TL below the therapeutic range).

Results: Out of 44 patients, 23 patients reached target TL, while 21 patients did not. Based on the TL, developments of ADAs, and clinical state of patients, recommendations were made to escalate the dose for 13 patients, switch therapy for 16 patients, de-escalate the dose for 10 patients, and continue therapy for 5 patients. Additionally, it was found that neutrophil count, erythrocyte sedimentation rate, and C-reactive protein were higher, and hemoglobin and packed cell volume were lower in patients who did not reach the target adalimumab TL ($p<0.05$).

Conclusions: Therapeutic drug monitoring for adalimumab can be an important tool for optimizing UC treatment and explaining the potential causes of non-responsiveness to this medicine.

Keywords

adalimumab, anti-drug antibodies, inflammatory bowel disease, therapeutic drug monitoring, ulcerative colitis

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Introduction

Inflammatory bowel diseases (IBDs), which include ulcerative colitis (UC) and Crohn's disease (CD), consist of chronic recurrent inflammatory diseases of unknown etiology that affect the gastrointestinal tract (GIT).[1] While the inflammation in UC is limited to the colon and rectum, the inflammation in CD can affect all parts of the GIT, from the mouth to the anus, and is linked to discontinuous transmural lesions of the gut wall.[2] Regardless of sex, IBD can start at any age; however, the most significant peak of onset occurs between the ages of 15 and 45. The incidence is steadily rising to the point that it qualifies as a global health issue.[3]

The pathogenesis of ulcerative colitis involves the activation of different immune cells, which results in the secretion of pro-inflammatory cytokines, i.e., tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IFN-γ, IL-6, and IL-23, which increases the permeability of the intestinal barrier and thus promotes inflammation in the intestinal mucosa.[4]

Tumor necrosis factor alpha (TNF-α) inhibitors are frequently employed in treating autoimmune diseases such as IBD (for both moderate-to-severe CD and UC).[5,6] Infliximab, adalimumab, golimumab, and certolizumab are TNF-α inhibitors that have been employed in the clinical setting of IBD; each has a unique pharmacological profile and varying efficacy.[5] They are utilized when other treatments are ineffective in improving the disease's signs and symptoms.[7] Despite anti-TNF-α biologics showing favorable therapeutic effects in achieving clinical, endoscopic, and histologic remission in IBD[8], they are not without drawbacks, namely a higher risk of serious infection and loss of response in 30–50% of patients.[9] This encompasses a gradual decline in responsiveness over time as well as an initial absence of response.[10] Additionally, response may be changed by patient variables (such as smoking status and the duration of the condition). Lastly, the response seems to be influenced by genetic differences.[11]

Three major mechanisms of biologic treatment failure have been proposed. The first one is the non-immune-mediated pharmacokinetic failure related to the rapid drug clearance. The second mechanism is the immune-mediated pharmacokinetic failure caused by the production of neutralizing anti-drug antibodies (ADAs) against biologics (presenting as secondary loss of response during the maintenance phase of biologics treatment). The third mechanism is the mechanistic failure where the IBD may be driven by inflammatory mechanisms not blocked by the applied biologics.[12]

Drug trough concentrations refer to measuring drug levels just before the subsequent dose.[13] Higher trough levels (TL) of the drug equate to higher exposure and result in better clinical outcomes.[14]

In order to optimize treatment for IBD and to achieve more demanding, objective end goals, therapeutic drug monitoring (TDM) has become a popular approach. Since low trough levels/concentrations or the development of ADAs are variously linked to treatment failure, the TDM of biological drugs includes measuring levels of serum drug concentrations and ADAs to explain primary non-response or secondary loss of response.[15]

The TDM can be implemented in two main ways: reactive TDM and proactive TDM. Reactive TDM involves measuring drug and ADAs levels in patients experiencing a primary non-response or secondary loss of response. This approach helps in rationalizing management by identifying reasons for treatment failure.[16] Proactive TDM, on the other hand, involves monitoring drug trough levels/concentrations at regular intervals in patients in remission to maintain therapeutic concentrations and potentially prevent loss of response.[17]

Adalimumab is a fully humanized IgG1 monoclonal antibody that is administered by the subcutaneous (SC) route. When used for UC, adalimumab is given at a dose of 160 mg (day 1), and then 80 mg 2 weeks later (day 15), followed by a maintenance dose (beginning week 4, day 29) of 40 mg SC every 2 weeks.[18] The recommended target TL of adalimumab at maintenance when used for IBD is 8–12 μg/mL.[19] In order to provide more individualized and efficient patient care, studies are still being done to determine the best way to use TDM in adalimumab therapy for IBD.[20]

Aim

This study aims to evaluate TL, the development of ADAs, and their relationships with clinical and laboratory variables in Iraqi patients with ulcerative colitis receiving adalimumab therapy.

Patients and methods

Study design

The research employed a cross-sectional observational design to examine the treatment outcomes of adalimumab in patients diagnosed with UC and on maintenance therapy. The patients received treatment in accordance with clinical practice guidelines and the severity of their diseases while being supervised by a gastroenterologist.[21]

Setting

The present study was conducted at the Gastroenterology and Hepatology Teaching Hospital, Medical City, Baghdad, Iraq, and lasted from April 2024 to November 2024.

Ethical consideration

The research proposal specifies the current study's goals, and the suggested data collection methodologies were sub-

mitted to the College of Pharmacy, University of Baghdad, with clearance from the Scientific and Ethical Committee (IDRECAUBCP742024k, date: 7-4-2024). The Iraqi Ministry of Health also gave its clearance. Informed consent was obtained from all individual participants included in the study. The participation was entirely voluntary, and no incentives were offered.

Inclusion criteria

The study included UC patients who were over 18 years of age and who had been previously diagnosed with UC. These patients received protocols of treatment prescribed by physicians at the Hepatology Teaching Hospital. All the patients were receiving maintenance treatment for more than three months with adalimumab + azathioprine + 5-aminosalicylic acid.

Exclusion criteria

Patients who had the following coexisting diseases were excluded: immune system disorders (rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and systemic lupus erythematosus). Other exclusions include Paget's disease, diabetes mellitus, asthma, chronic obstructive pulmonary disease, severe hepatic, cardiovascular, renal diseases and organ transplant recipients, and current cancer treatments or iron supplementation or the use of systemic or rectal steroids in the past 8 weeks.

Study groups

The total sample size of eligible ulcerative colitis patients was 44. A convenient sampling method was followed wherein all eligible participants were enrolled after verbal consent. The study used this sampling method due to the complexity of identifying and recruiting eligible participants based on inclusion and exclusion criteria, especially those related to specific treatments.

The eligible patients were allocated into two main groups: group 1 (patients with TL within or above the therapeutic range of 8–12 μg/mL) and group 2 (patients with TL below the therapeutic range). Patient response assessment (by physician) was done by using Partial Mayo Score (PMS). Score <2: remission. Score 2-4: mild activity. Score 5-7: moderate activity. Score >7: severe activity.[22]

Data collection

Demographic data such as age, sex, weight, height, disease duration, smoking status, family history, and previous biological therapy were collected via direct patient interviews using a patient data chart specially designed for this study.

Sample preparation and laboratory parameters

A 10-mL venous-blood sample was drawn from each patient. Blood samples were collected immediately before the next scheduled dose to confirm that trough levels were measured accurately and then split into three samples: one was taken in an erythrocyte sedimentation rate (ESR) tube for the ESR test, and the other was taken in an EDTA tube for the complete blood picture test. On the day of obtaining the sample, the complete blood count tests, ESR, and C-reactive protein (CRP) were carried out, and the last portion was left to clot. Later, centrifuging for 20 minutes at 2,000–3,000 rpm was used to remove the clot. Serum samples from the resulting supernatant were separated, stored in Eppendorf tubes, and preserved in a deep freezer at −80°C until the time of analysis of biomarkers. The ADVIA 120 Hematology System was used to perform an automated assay for measuring hemoglobin level, packed cell volume (PCV), mean platelet volume (MPV), and platelet count. ELISA testing had been carried out in step with the manufacturer's instructions. The TL of the adalimumab ELISA kit from Matriks Biotek [Turkey (Cat. ADA-SPEC-ADA.), detection limit (ng/mL) 18.75, spike recovery (%): between 85-115, precision: intra-assay and inter-assay CVs <30%]; the ADAs kit from Matriks Biotek [Turkey (Cat. ADA-QNS-HUM.), detection limit (ng/mL) 7.5, spike recovery (%): between 85-115, precision: intra-assay and inter-assay CVs <30%]; and the serum calprotectin (CALP) kit from Fine Test Biotech [China (Cat. No. EH4140), detection limit (sensitivity): 0.375 ng/mL, precision: Intra-assay and inter-assay CVs <30%] were used for the ELISA tests.

These tests are conducted using the sandwich type as the guiding premise, which are plate-based assays for detecting and quantifying a specific protein in a complex mixture. Concisely, standards and serum samples were incubated in the microtiter plate pre-coated with the human monoclonal ADAs for adalimumab detection, pre-coated with the adalimumab for anti-adalimumab antibody detection, and pre-coated with the human anti-CALP antibody for CALP detection. Standards and serum samples were added and bound to antibodies coated on the wells and then incubated. After incubation, wash buffer removed unbound conjugates. Then, (for CALP detection) biotinylated detection antibody was added to bind with CALP conjugated on the coated antibody. After washing off unbound conjugates, HRP-streptavidin was added and bound to either adalimumab, ADAs, or CALP. Following incubation, the wells were washed, and the bound enzymatic activity was detected by the addition of the tetramethylbenzidine (TMB) chromogen substrate. To end, the reaction terminated with an acidic stop solution. The color developed is proportionate to the amount of free adalimumab, ADAs, and CALP in the sample or standard. The wavelength at which the absorbance was measured was 450 nm. After that, the proportional measurement of concentration in the samples was determined using the standard curve.[23-25]

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Statistical analysis

The Shapiro-Wilk test was used to evaluate if a variable follows a normal distribution. Variables that follow a normal distribution were given as mean and standard deviation (SD), while variables that do not follow a normal distribution were stated as median and interquartile range (IQR). When the variables had a normal distribution, the difference between Group 1 and Group 2 was evaluated using an independent t-test. If the data did not, a Mann-Whitney U test was used. The chi-square test was used to determine the difference between categorical variables. The binary logistic regression analysis was used to determine the relationship between various factors and TL attainment. All statistical analyses were performed using SPSS 27 (Chicago, USA), and *p*-values less than 0.05 were considered significant.

Results

Demographic and disease characteristics differences between groups

Table 1 demonstrates the patient demographic and disease characteristics of 44 UC [23 patients with trough levels within or above the therapeutic range (Group 1), 21 patients below the therapeutic range (Group 2)]. Patients included 18 females (40.9%) and 26 males (59.1%), with no statistically significant difference found between the groups in both sexes ($p>0.05$).

The mean age of the study groups was 36.83±14.721 years for patients in Group 1 and 37.43±12.396 years for patients in Group 2, with no statistically significant difference found between the groups ($p>0.05$).

The mean BMI for patients in Group 1 and Group 2 was 27.464±4.586 kg/m^2 and 24.373±4.648 kg/m^2, respectively. The BMI was significantly higher in group 1 patients compared to group 2 ($p=0.042$).

The median for duration of the disease for UC patients in group 1 and group 2 was 5.50 (3.00-9.00) years and 6.00 (4.00-9.00), respectively. No significant difference was found between UC groups with respect to the duration of the disease ($p>0.05$).

Regarding the biological treatment, the study included 25 naive patients (56.8%) and 19 patients with previous biological treatment (43.2%), with no statistically significant difference found between the groups ($p>0.05$).

A significant association between response and achievement of TL was found between UC groups [a higher number of patients achieved remission in group 1 compared to group 2 ($p=0.035$)].

Classification of the patients with recommendations based on TL, ADAs, and disease activity

Table 2 shows the patient classification and recommendations based on TL, ADAs, and disease activity, with recommendations to escalate the dose for 13 patients (29.55%), switch therapy for 16 patients (36.36%), de-escalate the dose for 10 patients (22.73%), and continue therapy for 5 patients (11.36%). Out of 44 patients, the results of the current study showed that 6 patients had low TL with negative ADAs and were in active disease (non-immune pharmacokinetic failure), and 7 patients had low TL and were in remission. Concerning these patients, it is therefore advised

Table 1. Demographic and clinical data of the study participants

Variable		Group 1 (23 patients)	Group 2 (21 patients)	Statistical test [t(df), U, χ^2 (df)] at 95% CI	*P*-value
Sex	Female, n (%)	8 (18.2)	10 (22.7)	$\chi^2(1)=0.748$	0.387
	Male, n (%)	15 (34.1)	11 (25.0)		
Age, year (mean±SD)		36.83±14.721	37.43±12.396	t(42)=−0.146	0.885
BMI, kg/m^2 (mean±SD)		27.464±4.586	24.373±4.648	**t(40.66)=2.097**	**0.042***
Duration of disease, year (median ± IQR)		5.50 (3.00–9.00)	6.00 (4.00–9.00)	U=229.50	0.618
Biological treatment	Naïve, n (%)	14 (31.8)	11 (25.0)	$\chi^2(1)=0.322$	0.570
	Previous biological treatment, n (%)	9 (20.5)	10 (22.7)		
Response	Remission, n (%)	15 (34.1)	7 (15.9)	**$\chi^2(1)=4.464$**	**0.035***
	Active, n (%)	8 (18.2)	14 (31.8)		

* significant difference ($p<0.05$). Two-sample t-test [t(df)] was used for statistical analysis of age and BMI, the Mann-Whitney U test was used for statistical analysis of the duration of the disease, and the chi-square test (χ^2) was used for statistical analysis of sex, biological treatment, and response. BMI: body mass index; CI: confidence interval of the difference; df: degree of freedom; IQR: interquartile range; SD: standard deviation; TL: trough level; UC: ulcerative colitis

Table 2. Classification of UC patients and the recommendations made based on their TL, ADAs, and disease activity

Patients with TL below the therapeutic range (21 patients)			**Patients with TL within or above the therapeutic range (23 patients)**		
Seven patients in remission	Fourteen patients with active diseases		Fifteen patients in remission		Eight patients with active disease
Seven patients with negative ADAs	Six patients with negative ADAs (non-immune ph. k. failure)	Eight patients with high positive ADAs (Immune ph. k. failure)*	Five patients within therapeutic range	Ten patients above the therapeutic range	Eight patients with mechanistic failure
Recommendations made					
Escalate the dose or shorten the interval between doses.	Escalate the dose or shorten the interval between doses	Switching therapy	Continue therapy	De-escalate the dose or lengthen the interval between doses	Switching therapy

ADAs: anti-drug antibodies; ph. k.: pharmacokinetic; * Those who have low trough levels and high titers of anti-drug antibodies.

to receive higher doses of their medications or shorter intervals between doses and monitor response.

Furthermore, there were 8 patients in active disease despite achieving target TL who needed to switch therapy (mechanistic failure happens when the patient does not respond despite optimum drug TL). In addition, 8 patients who did not achieve target TL were in active disease with high positive ADAs and also need to switch therapy (immune pharmacokinetic failure happens in patients who have low or undetectable TL and high levels of ADAs). Moreover, 5 patients were in remission state with the achievement of target TL (need to continue therapy), and 10 patients were in remission state with TL above the target (need to de-escalate the dose or lengthen the interval between doses).

Differences between groups according to disease activity, TL, ADAs, and other laboratory variables

Table 3 shows the differences between group 1 and group 2 UC patients in different variables. The PMS shows no signif-

Table 3. Difference between UC patients with TL within or above the therapeutic range (Group 1) and patients with TL below the therapeutic range (Group 2) according to different variables

Variable	**Group 1 (23 patients)**	**Group 2 (21 patients)**	**Statistical test [t(df), U] at 95% CI**	***P*-value**
PMS	1 (1-6)	2 (1-5.5)	U=174.50	0.104[b]
TL (µg/mL)	12.78 (9.53-17.43)	2.760 (0.66-5.68)	U=2.00	**<0.001**[*b]
ADAs (ng/mL)	16.03 (7.56-35.18)	268.09 (17.74-1264.74)	U=116.00	**0.003**[*b]
HGB (g/dL)	12.98±2.08	11.476±1.82	t(41.92)=2.55	**0.014**[*a]
PCV (%)	39.71±4.75	35.25±5.52	t(39.65)=2.855	**0.007**[*a]
MCV (fL)	80.31±6.96	78.73±8.29	t(42)=0.684	0.498[a]
WBC count (*10^3/µL)	6.92±1.97	7.91±2.53	t(42)=−1.457	0.153[a]
LYM count (*10^3/µL)	2.62±0.818	2.18±0.93	t(42)=1.686	0.099[a]
NEUT count (*10^3/µL)	3.570±1.280	4.67±1.448	t(40.14)=−2.663	**0.011**[*a]
PLT count (*10^3/µL)	251 (203-339)	366 (292-366)	U=188.50	0.213[b]
MPV (fL)	9.52±1.39	8.39±1.02	t(42)=1.789	0.081[a]
ESR (mm/hr)	22.00 (9.00-31.00)	32.00 (14.50-66.00)	U=145.50	**0.024**[*b]
CRP (mg/L)	9.28 (5.87-16.00)	19.90 (7.86-62.50)	U=134.50	**0.012**[*b]
CALP (ng/mL)	4284.91±1196.44	4767.42±1415.80	t(42)=−1.225	0.228[a]

* significant difference ($p<0.05$). [a] A two-sample t-test [t(df)] was used, and the data presented as mean ± SD. [b] Mann-Whitney U test was used, and the data presented as median (IQR). ADAs: anti-drug antibodies; CALP: calprotectin; CI: confidence interval of the difference; CRP: C-reactive protein; df: degree of freedom; ESR: erythrocyte sedimentation rate; HGB: hemoglobin; LYM: lymphocyte; MCV: mean corpuscular volume; MPV: mean platelet volume; NEUT: neutrophil count; PCV: packed cell volume; PLT: platelet; PMS: Partial Mayo Score; TL: trough level; WBC: white blood cells.

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icant differences between patients in both groups (p>0.05). The TL was significantly higher in-group 1 compared to group 2 (p≤0.001). While the level of ADAs was significantly higher in-group 2 compared to group 1 (p=0.003).

In addition, HGB and PCV were significantly higher in group 1 compared to group 2 (p=0.014 and 0.007, respectively). While there was no significant difference in the MCV between the groups (p>0.05).

The levels of WBC, lymphocyte count, PLT, and MPV showed no significant differences between the groups (p>0.05). On the other hand, there was a significantly lower level of neutrophil count in group 1 compared to group 2 (p=0.011).

The levels of ESR and CRP were significantly lower in group 1 compared to group 2 (p=0.024 and 0.012, respectively). The level of serum calprotectin was lower in UC patients in group 1 than patients in group 2, in spite of not being statistically significant(p>0.05).

Target TL achievement association and prediction by univariate and multivariate regression analysis

Using univariate binary logistic regression, only ESR, BMI, CRP, HGB, PCV, and neutrophil count had a significant effect on reaching the goal TL (p<0.05) **(Table 4)**.

While in multivariate binary regression (backward technique) that includes ESR, CRP, HGB, BMI, PCV%, and neutrophil count variables, only the model containing PCV% (positive association), neutrophil count, and CRP (negative association) had a significant effect on reaching the goal TL [OR=0.773 (0.627-0.954), p=0.016], [OR=1.958 (1.070-3.585), p=0.029], and [OR=1.062 (1.000-1.128), p=0.049], respectively **(Table 5)**.

Discussion

In the current study, 44 UC patients receiving adalimumab were included. Therapeutic drug monitoring was used to assess adalimumab TL and the existence of ADAs to adalimumab, which can help with therapy optimization. The observed differences in patients' outcomes directly informed clinical recommendations, with a significant proportion of patients requiring a change in treatment strategy. This highlights the potential for using these markers to stratify patients early in their treatment, leading to more timely and effective therapeutic adjustments and potentially improving overall outcomes.

Concerning the TL, ADAs, and disease activity of the patients, recommendations were made to increase the dose or shorten the intervals between doses and monitor the response for patients who had low TL with negative ADAs and were in active disease (non-immune pharmacokinetic failure) and for patients who had low TL and were in remission.[26,27] Furthermore, recommendations were made to switch therapy for patients who were in active disease despite achieving target TL (mechanistic failure) and for

Table 4. Target TL achievement association and prediction by univariate analysis for UC patients

	Univariate analysis [a]			
Variable	**OR [EXP(B)]**	**95% CI for EXP(B)**		***p*-value**
		Lower	**Upper**	
PMS score	1.101	0.872	1.390	0.418
BMI (kg/m^2)	0.871	0.871	0.998	**0.047***
ADAs (ng/mL)	1.007	1.000	1.014	0.052
HGB (g/dL)	0.675	0.4830	0.944	**0.022***
PCV (%)	0.842	0.736	0.963	**0.012***
MCV (fL)	0.972	0.898	1.053	0.488
WBC count (*10^3/µL)	1.226	0.925	1.624	0.157
LYM count (*10^3/µL)	0.548	0.265	1.130	0.103
NEUT count (*10^3/µL)	1.821	1.110	2.986	**0.018***
PLT count (*10^3/µL)	1.004	0.997	1.010	0.256
MPV (fL)	0.624	0.362	1.076	0.090
ESR (mm/hr)	1.037	1.005	1.069	**0.021***
CRP (mg/L)	1.048	1.004	1.093	**0.020***
CALP (ng/mL)	1.000	1.000	1.001	0.225

* significant difference; [a] Binary logistic regression is used (Enter). ADAs: anti-drug antibodies; BMI: body mass index; CALP: calprotectin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HGB: hemoglobin; LYM: lymphocyte; MCV: mean corpuscular volume; MPV: mean platelet volume; NEUT: neutrophil; PCV: packed cell volume; PLT: platelet; PMS: Partial Mayo Score; TL: trough level; WBC: white blood cells

Table 5. Target TL achievement prediction by multivariate analysis for UC patients

Multivariate analysis [b]				
Variable	**OR [EXP(B)]**	**95% CI for EXP(B)**		***P*-value**
		Lower	**Upper**	
BMI (kg/m^2)	0.934	0.770	1.133	0.489 NS
HGB (g/dL)	1.519	0.643	3.590	0.341 NS
PCV (%)	0.773	0.627	0.954	**0.016***
NEUT Count (*10^3/μL)	1.958	1.070	3.585	**0.029***
ESR (mm/hr)	0.972	0.923	1.023	0.271 NS
CRP (mg/L)	1.062	1.000	1.128	**0.049***

* significant difference; NS: non-significant difference; [b] Binary logistic regression was used (backward technique). BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HGB: hemoglobin; NEUT: neutrophil; PCV: packed cell volume.

patients who did not achieve target TL and were in active disease with high positive ADAs (immune pharmacokinetic failure).[28] Additionally, for patients who were in remission with the achievement of target TL, recommendations were made to continue therapy, and for those who were in remission with TL above the target, recommendations were made to de-escalate the dose or lengthen the interval between doses. Studies in real-world settings continue to confirm TDM effectiveness with observed clinical remission rates. The optimal adalimumab TL for UC are often considered similar to those for CD, aiming for levels associated with mucosal healing and sustained remission.[28-31]

Additionally, the current study shows that ADAs were higher in patients with TL below the therapeutic range when compared to patients with TL within or above the therapeutic range. A Saudi cohort study (n=392 IBD patients receiving anti-TNF therapy, including adalimumab): ADAs were negative in 73.1% of patients and weakly positive in 9.8%; 17.1% of patients had positive ADAs, with sub-therapeutic anti-TNF drug levels significantly associated with ADAs positivity (p<0.001).[32]

Furthermore, routine inflammatory markers (CRP and ESR) and routine blood tests (HGB, PCV, MCV, white blood cell count, lymphocyte count, neutrophil count, MPV, and platelet count) were examined in the current study. It was found that neutrophil count, ESR, and CRP were higher, and HGB and PCV were lower in patients with TL below the therapeutic range. An IBD cohort study published in 2020 showed a significant negative correlation between anti-TNF trough levels and some laboratory markers, including serum CRP.[33] According to a study by Roblin et al., a combination of CRP, TL, and ADAs can be used to accurately predict a loss of response to infliximab.[34] Also, the current study demonstrates that CRP could be used as a new noninvasive biomarker to predict a loss of response to adalimumab. Moreover, and for routine disease activity assessment, the recent guidelines for UC management suggest measuring CRP and fecal calprotectin in asymptomatic patients to avoid more expensive and invasive testing, such as endoscopy.[35] For IBD patients achieving mucosal healing, their WBC count, PLT count, ESR, CRP, and neutrophil/lymphocyte ratio levels were significantly lower than those in patients that did not achieve mucosal healing (all p<0.05) and could be used as noninvasive markers for predicting mucosal healing in patients with IBD.[36] Anemia (low HGB and PCV) is highly prevalent in IBD patients and directly linked to chronic inflammation.

The higher level of HGB and PCV in patients with TL within or above the therapeutic range is consistent with a prior study showing that anti-TNF treatment, such as adalimumab, raises HGB levels and lowers anemia rates in IBD patients. This benefit occurred concurrently with a decrease in disease activity measured by CRP and was unrelated to iron supplementation during treatment.[37]

Calprotectin is an acute-phase protein that regulates neutrophil migration. Its quantity corresponds with neutrophil migration and indicates the intensity of inflammation in IBD.[38]

However, this is the first study, to the best of our knowledge, to examine the association between serum CALP and adalimumab TL and find that serum CALP was higher in UC patients with TL below the therapeutic range, in spite of not being statistically significant. A previous study in Japan (2019) found that serum CALP is an inflammatory biomarker in IBD, but it might be more effective in evaluating CD patients than UC patients.[39]

A recent Iraqi study by Saleh HH et al. concluded that serum CALP is a new marker that could be used in evaluating and predicting how well CD patients will respond to infliximab and achieve target infliximab TL.[40]

Study limitations

The present study is not without its limitations, which can be enumerated as follows: firstly, the sample size is limited; secondly, TDM results (TL and ADAs) were delayed because samples were obtained from patients and stored for approximately six months before laboratory measurements were completed, resulting in delayed therapy recommendations to physicians and patients.

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Conclusion

Therapeutic drug monitoring for adalimumab (through the measurement of TL and ADAs) has the potential to serve as a valuable instrument in formulating suitable recommendations to optimize UC treatment (escalating the dose for 13 patients, switching therapy for 16 patients, de-escalating the dose for 10 patients, and continuing therapy for 5 patients). Multivariate analysis of the studied variables indicates that PCV, neutrophil count, and CRP could serve as indicators to predict TL accomplishment and subsequent response to adalimumab therapy.

Ethical approval

Ethical approval for the study was granted by the Scientific and Ethical Committee of the College of Pharmacy in the University of Baghdad (Protocol IDRECAUBCP742024k, date: 7-4-2024). The Iraqi Ministry of Health also gave its clearance.

Conflict of interest

The authors have declared that they have no conflict of interest, financial or otherwise.

Ethical statements

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- Informed consent was obtained from all individual participants included in the study, and participation was entirely voluntary, with no incentives offered.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Use of AI

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Author contributions

Each named author has substantially contributed to conducting the underlying research and drafting this manuscript—conceptualization and methodology: AM and DJ; investigation: AM, RJ; formal analysis: AM and DJ; visualization and writing–original draft: AM and DJ; project administration: AM, DJ, and RJ; writing–review and editing: AM, DJ, and RJ; funding acquisition: AM; supervision: DJ, RJ. All authors have read and agreed to the final version of the manuscript and have agreed to the Folia Medica's submission policies.

Data availability

All data used are referenced or included in the article.

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