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Therapeutic Drug Monitoring of Infliximab in Iraqi Patients with Moderate to Severe Ulcerative Colitis

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Abstract

The term "inflammatory bowel disease" refers to a group of gastrointestinal tract inflammatory disorders that are considered idiopathic, chronic, and relapsing. Infliximab, a chimeric monoclonal antibody, is a medication used to treat a number of autoimmune diseases. Therapeutic drug monitoring is a tool used in therapeutic decision-making that allows dosage modifications to be made in accordance with clinical and laboratory measures, usually blood concentrations of the drug, in order to achieve the drug exposure linked to the best response rate. The trough concentrations of infliximab at 3 to 7 µg/mL is most effective at inducing remission in patients with inflammatory bowel disease. The aims of the current study were to determine the achievement of trough level target, development of antidrug antibodies to Infliximab, assess response to therapy and to study trough level relation with different variables in patients with ulcerative colitis. The present study was cross-sectional conducted at "Gastroenterology and Hepatology Teaching Hospital/ Medical City / Baghdad / Iraq" during May 2022 to November 202٢. Forty candidate patients with ulcerative colitis were included. According to trough level, disease activity and development of antibodies, escalation of the dose were recommended for 10 patients (25%), switching therapy were recommended for 16 patients (40%), and continuation of the same dosage regimen were recommended for 14 patients (35%). In addition, results of current study showed that age, body mass index, and packed cell volume were significantly higher and erythrocyte sedimentation rate was significantly lower in in patients achieved target infliximab trough level compared to those not achieved. By using multivariate binary regression analysis only age and erythrocyte sedimentation rate can be used to predict the achievement of target trough level of infliximab. In conclusion, therapeutic drug monitoring of infliximab to determine the trough level and antidrug antibodies can explain the possible causes of non-responsiveness to this drug among ulcerative colitis patients with subsequent recommendations based on these findings.

Keywords: Antidrug antibodies, Infliximab, Therapeutic drug monitoring, Trough level, Ulcerative colitis.

Introduction

The term "inflammatory bowel disease" (IBD) refers to a group of gastrointestinal tract (GIT) inflammatory disorders that are considered idiopathic, chronic, and relapsing. Inflammatory bowel disease is widespread in developed countries[(1)]. Globally, the incidence of IBD varies from-24.5 per 100,000 person-years[(2)]. In Iraq, the prevalence of IBD was 1.3%[(3)]. The exact cause of IBD is not well known. Dysregulation of the inflammatory response within the GIT, genetic predisposition, and environmental or antigenic factors are thought to be involved[(4, 5)]. The two primary disorders that comprise IBD are Crohn's disease (CD) and ulcerative colitis (UC)[(6, 7)]. Ulcerative colitis is restricted to rectum and colon and present as inflammatory changes that include the colonic mucosa in a continuous superficial manner, usually initiating in the rectum and extending proximally[(8, 9)].

With UC, the inflammatory pattern is continuous and exacerbated in all affected gastrointestinal tract segments. The inflammation is observed to be superficial and usually does not penetrate the GIT's submucosal layer [(6, 10)] (Figure 1)[(11)]. The formation of crypt abscesses inside the GIT's mucosal layers is one of UC's defining characteristics, and it may aid to differentiate the condition from CD[(12)]. Excessive inflammation can also lead to hypertrophied GI mucosa in certain areas, which can be recognized as colon pseudopolyps[(13)].

Infliximab, a chimeric monoclonal antibody, is a medication used to treat a number of autoimmune diseases such as CD, UC, rheumatoid arthritis, psoriasis[(14, 15)]. Infliximab mechanism of action is by targeting

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TNF-α. Reduction in TNF-α activity is associated with improvement in the underlying inflammatory chest pain, hypotension, and dyspnea[6]. Several clinical factors, including shorter duration of disease, younger age of patients, no previous IBD-related surgery or stricturing phenotype, higher C-reactive protein level, no previous failing corticosteroids or immunomodulators, no history of smoking, and optimized trough level (TL) of anti-tumor necrosis factor (TNF) agent, have been associated with and predict better anti-TNF agent response in patients with IBD[16-18]. Other markers that may have a role to predict the response to Infliximab such as increased mean platelet volume (MPV), decreased serum oncostatin m (OSM), decreased serum calprotectin (CALP), increased platelet (PLT)[19-22].

Therapeutic drug monitoring (TDM) is a tool used in therapeutic decision-making that allows dosage modifications to be made in accordance with clinical and laboratory measures, usually blood concentrations of the drug, in order to achieve the drug exposure linked to the best response rate[23]. In the event of drug failure, there are 3 possible causes: Mechanistic failure occurs when the patient is not responding despite optimal drug TL. This type of failure is likely related to the disease process being driven by inflammatory mediators that are not blocked by the particular drug. Non-immune-mediated pharmacokinetic failure occurs when patients do not adequately respond to therapy in the setting of subtherapeutic TL and absence of process. Adverse effects of IV infliximab may include infusion - related reactions such as fever, neutralizing anti-drug antibodies (ADAs). Immune-mediated pharmacokinetic failure occurs in patients who have low or undetectable TL and high titers of ADAs. This type of drug failure results from the immune-mediated formation of neutralizing ADAs[24].

The Trough Concentration Adapted Infliximab Treatment (TAXIT) trial demonstrated that maintaining infliximab TL at 3 to 7 µg/mL is most effective at inducing remission in patients with IBD, with fewer flares than clinic-based dosing[25].Therapeutic drug monitoring can be carried out in two ways: "proactive" when it is done in patients who are in remission to potentially prevent future flare-ups and loss-of-response, or "reactive" when it is done in response to unsatisfactory disease control. Reactive TDM, when applied in during the course of an active illness, can direct treatment and provide insight into the mechanism underlying primary or secondary loss of response to a biologic drug. In order to optimize drug concentration at particular times, proactive TDM involves measuring TL and ADA levels[26]. This study is intended to determine the achievement of TL target, development of ADAs to Infliximab, assess response to therapy and to study TL relation with different variables in patients with ulcerative colitis.

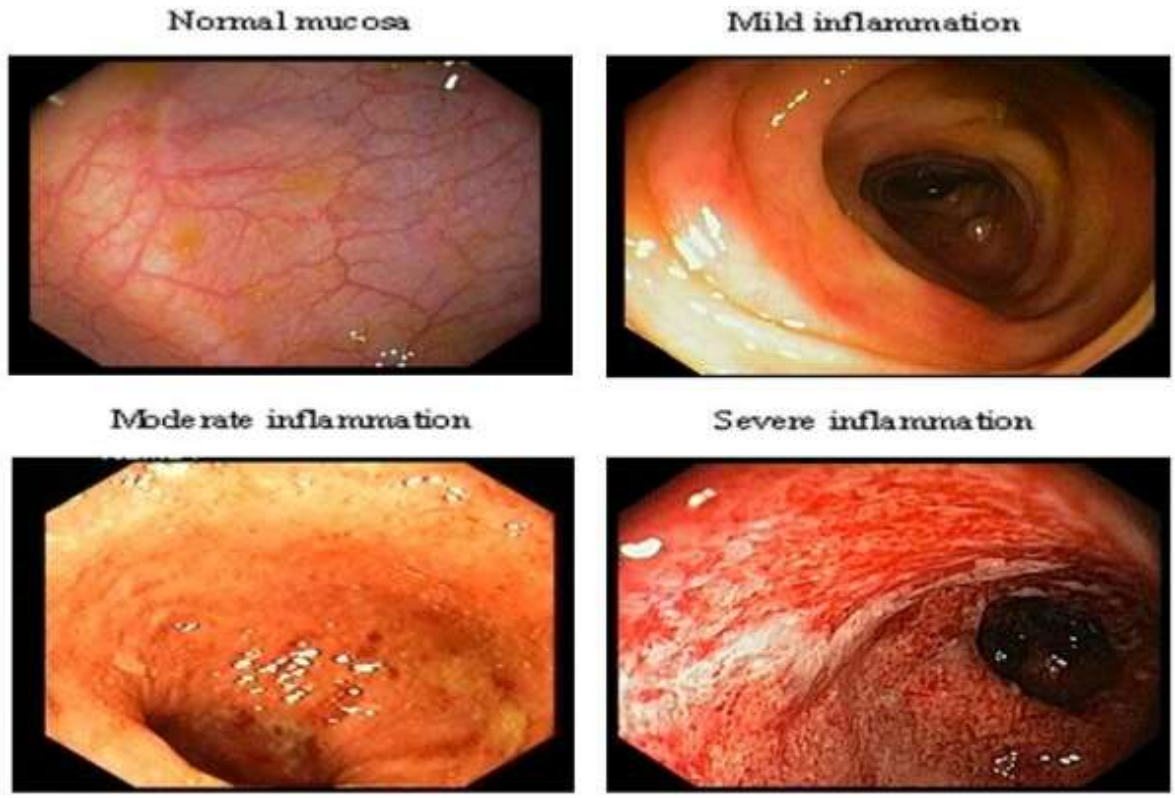

Figure 1. Endoscopic images of ulcerative colitis[11]

Patients, Materials and Methods

Study Design and Population

The present study was cross-sectional included 40 patients which conducted at "Gastroenterology and Hepatology Teaching Hospital/ Medical City / Baghdad / Iraq" during May 2022 to November 2022. Under the guidance of a gastroenterology specialist, the patients received treatment (Infliximab (Remsima®) 5mg/kg every 8 weeks + azathioprine (Imuran®) 50 twice daily+ 5-aminosalicylic acid 1g four times daily). based on the clinical practice guidelines and disease severity[27, 28].

Inclusion Criteria

- Age over 18 years.
- Patients who are diagnosed with moderate to severe UC according to Truelove and Witts' severity index [29].
- Patients on standard therapy (Infliximab (Remsima®) 5mg/kg+ azathioprine (Imuran®) 50 twice daily+ 5-aminosalicylic acid 1g four times daily).
- All patients on maintenance infliximab doses and complete the induction doses.

Exclusion Criteria

- Patients with other immune system disorders.
- Use of systemic or rectal steroids in the past 8 weeks.

Study groups

The eligible patients were allocated into two main groups:

Group 1: Include patients achieved target infliximab TL.

Group 2: Include patients not achieved target infliximab TL.

Response assessment done by using Partial Mayo Score (PMS) score: remission < 2 and active disease ≥ 2[30].

Sample collection and biomarkers testing

For each patient, 10 milliliters of venous blood were drawn using a single-use, plastic syringe. The sample was withdrawn immediately before the next dose of infliximab. Six milliliters of blood were centrifuged at 3000 rpm for ten minutes in a simple disposable tube containing gel and clot activator after being allowed to clot. 1.28 ml was collected in an erythrocyte sedimentation rate (ESR) tube for the ESR test, and two ml was utilized in a k3 EDTA tube for the complete blood picture test. The sample was stored in the National Center for Educational Laboratories- Medical city. The serum samples were kept in Eppendorf tubes at a temperature of -80°C until they were needed for the other assays. With the ADVIA 120 Haematology System's automated assay, the levels of haemoglobin, packed cell volume (PCV), mean platelet volume (MPV), and platelets were estimated. A blood sample of 175µL was placed in the Haematology System to be analyzed.

The Mixrate-X20 device was utilized to perform an automated test in order to measure the erythrocyte sedimentation rate. Using 1.28 milliliters of the blood sample were put into the ESR autoanalyzer for examination. The completion time for the results is 30 minutes, which is equivalent to one hour according to the Westergren reference method. For men and women, respectively, the reference range is (≤ 15 mm/hr) and (≤ 20 mm/hr)[31]. The tests for TL (Matriks Biotek, Turkey), ADA (Matriks Biotek, Turkey), OSM (Elabscience Biotechnology/ China) and CALP (Elabscience Biotechnology/China) concentration was determined by using ELISA test according to manual procedure notes of the ELISA kits. This test was designed with the sandwich type as its principle. Automatic ELISA reader PKL PPC 230 (Paramedical / Italy) was used to read the results of ELISA tests. At a wavelength of 450 nm, the absorbance was calculated. Following that, using the standard curve, the concentration in the samples was determined proportionally[32-35].

Statistical analysis

Continues variable assessed for adherence to normality using Shapiro-Wilk test, and variables followed normal distribution expressed as mean and standard deviation (SD), and those did not follow normal distribution expressed using their median and interquartile range (IQR). Independent t-test was used to assess difference between achieved TL group and not achieved TL group when variables followed normal distribution, if data did not adhere to normality Mann Whitney U test is used. Chi-square test used to assess difference between categorical variables. Binary logistic regression analysis (backward method) was used to assess the relationship between TL achievement and various predictors. Receiver operating characteristic (ROC) analysis was used to determine best cut-off value (cut-off value determined by Youden index), sensitivity, specificity for prediction of TL achievement. All analysis carried out using SPSS 27 (Chicago, USA) and p-value considered significant if <0.05.

Results

Patients' demographic and disease characteristics for both groups are presented in (Table 1). The means of body mass index (BMI) and age were significantly higher in group 1 patients compared to group 2 patients. No significant differences were found in all of the remaining variables. In addition, significantly higher number of patients in group 1 achieved remission compared to group 2.

Table 1. Difference between patients achieved target level (Group 1) and patients not achieved target level (Group 2) according to demographic and disease characteristics of the patients.

Variable	Group 1	Group 2	P-value
Gender			
Female [n (%)]	11 (52.4)	9 (47.4)	0.752^{NS}
Male [n (%)]	10 (47.6)	10 (52.6)	
Age(year) [median (IQR)]	34.00 (31.00-46.00)	30.00 (25.00-36.00)	0.022*
BMI (kg/m^2) [mean ± SD]	27.12 ± 4.93	24.07 ± 3.32	0.029*
Duration of disease(year) [median (IQR)]	4.00 (2.00-6.00)	7.00 (2.00-10.00)	0.503^{NS}
No. of Dose [median (IQR)]	7.00 (5.00-10.50)	8.00 (7.00-12.00)	0.282^{NS}
Response			
Remission [n (%)]	14 (66.7)	6 (31.6)	0.027*
Active [n (%)]	7 (33.3)	13 (68.4)	

BMI: body mass index; **IQR:** interquartile range; **NS**: No significant differences (P>0.05), (*) Significant difference (P<0.05).

Two-sample *t*-test was used for statistical analysis of BMI. Mann Whitney U test was used for statistical analysis of (age, no. of dose, duration of the disease).Chi-square test was used for statistical analysis of (gender, response).Classification of patients and the recommendations made based on (TL, ADAs, and disease activity) are shown in (Table 2) where the recommendations to escalate the dose were made for 10 patients (25%), to switch therapy for 16 patients (40%), and to continue therapy for 14 patients (35%).

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

Patients NOT achieved target level (19 patients)				Patients achieved target level (21 patients)	
6 in remission	**13** with active diseases			**14** in remission	**7** with active disease
	1 with negative ADA (Non-immune pharmacokinetic failure)	**3** with Low positive ADA (immune pharmacokinetic failure)	**9** with high positive ADA (immune pharmacokinetic failure)		Mechanistic failure
Recommendations made					
Escalate the dose	Escalate the dose	Escalate the dose	Switching therapy	Continue therapy	Switching therapy

The TL and PCV were significantly higher in group 1 patients compared to group 2 patients while the ESR level was significantly higher in group 2 patients compared to group 1 patients. Other biomarkers show no significant differences as shown in (Table 3).

Table 3. Difference between patients achieved target level (Group 1) and patients not achieved target level (Group 2).

Variable	Group 1	Group 2	P-value
PMS	1.00 (1.00-5.00)	4.00 (1.00-7.00)	0.105^{NSb}
HGB (g/dL)	12.20 ± 1.13	11.17 ± 2.03	0.062^{NSa}
PCV (%)	38.75 ± 4.62	35.21 ± 4.70	0.021^{*a}
MPV (fL)	8.27 ± 1.10	8.31 ± 1.00	0.908^{NSa}
ESR (mm/hr)	14.00 (7.00-21.00)	29.00 (20.00-45.00)	<0.001^{**b}
CRP (mg/dL)	1.70 (0.51-3.93)	2.32 (0.81-8.80)	0.069^{NSb}
ALB (g/dL)	4.97 (4.48-5.09)	4.88 (4.40-5.02)	0.226^{NSb}
OSM (pg/ml)	139.40 (80.33-534.92)	212.57 (94.52-992.98)	0.215^{NSb}

Continued table 3

Variable	Group 1	Group 2	P-value
CALP (ng/mL)	1018.20 (920.45-1137.20)	990.80 (905.40-1166.70)	0.979^{NSb}
TL (µg/mL)	3.94 (3.47-5.48)	1.60 (0.84-2.36)	$<0.001^{**b}$
ADA (ng/mL)	57.82 (43.62-88.39)	62.15 (49.11-88.92)	0.748^{NSb}
PLT(*10^3)	270.00 (240.50-306.00)	290.00 (267.00-343.00)	0.057^{NSb}

(*) Significant difference (P<0.05).
([a])Two-sample *t*-test was, used data presented as mean ± SD.
([b]) Mann Whitney U test was used, data presented as median (IQR).
ADA: anti-drug antibody; **ALB:** albumin; **CALP**: calprotectin; **CRP**:C-reactive protein; **ESR**: erythrocyte sedimentation rate; **HGB**: hemoglobin; **MPV**: mean platelet volume; **NS**: No significant differences (P>0.05); **OSM**: oncastatin-m; **PCV**: packed cell volume; **PLT**: platelet; **PMS**: Partial mayo score; **TL**: trough level.

By using univariate binary logistic regression only PCV, ESR, age, and BMI show significant effect. While in multivariate binary regression (backward method) contain PCV, ESR, age, and BMI variables, only model contain ESR and age had significant effect on achievement of TL target as shown in (Table 4).

Table 4. Trough level target achievement prediction by different variables.

	Univariate analysis[a]		Multivariate analysis[b]	
Variable	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age	0.926 (0.862-0.995)	0.036^{*}	0.893 (0.803-0.993)	0.036^{*}
BMI	0.827 (0.688-0.994)	0.043^{*}		
PMS	1.191 (0.907-1.563)	0.208^{NS}		
ADA (ng/mL)	1.007 (0.994-1.019)	0.279^{NS}		
HGB (g/dL)	0.660 (0.424-1.027)	0.066^{NS}		
PCV (%)	0.844 (0.724-0.984)	0.030^{*}		
MPV (fL)	1.037 (0.567-1.899)	0.905^{NS}		
ESR (mm/hr)	1.106 (1.030-1.186)	0.005^{**}	1.121 (1.037-1.211)	0.004^{**}
CRP (mg/dL)	1.167 (0.965-1.413)	0.112^{NS}		
ALB (g/dL)	0.463 (0.099-2.151)	0.326^{NS}		
OSM (pg/ml)	1.001 (1.000-1.002)	0.213^{NS}		
CALP (ng/mL)	1.000 (0.995-1.005)	0.959^{NS}		
PLT (*10^3)	1.009 (0.999-1.018)	0.077^{NS}		

(*) Significant difference (P<0.05).
([a]) Binary logistic regression is used
([b]) Binary logistic regression (backward method) is used
ADA: anti-drug antibody; **ALB:** albumin; **BMI**; body mass index; **CALP**: calprotectin; **CRP**:C-reactive protein; **ESR**: erythrocyte sedimentation rate; **HGB**: hemoglobin; **MPV**: mean platelet volume; **NS**: No significant differences (P>0.05); **OR**: Odds Ratio; **OSM**: oncastatin-m; **PCV**: packed cell volume; **PLT**: platelet; **PMS**: Partial mayo score.

By using ROC analysis to determine the best cut-off value (cut-off value determined by Youden index) that can be used to predict target level achievement. The cut-off value for PCV was ≥36.25 with sensitivity=76.2%, specificity=63.2% and, AUC=0.682 and for ESR was ≤ 24.00 with sensitivity=85.7%, specificity=68.4% and, AUC= 0.799 as shown in (Table 5).

Table 5. ROC Curve Analysis

Variable	Cut-off	Sens.	Spec.	AUC	P-value	CI 95
PMS	1.50	66.7%	68.4%	0.650	0.104^{NS}	0.475-0.826
HGB (g/dL)	11.25	81%	52.6%	0.672	0.064^{NS}	0.494-0.849
PCV (%)	≥36.25	76.2%	63.2%	0.682	0.049^{*}	0.511-0.853
MPV (fL)	8.75	38.1%	78.9%	0.462	0.685^{NS}	0.279-0.646
ESR (mm/hr)	≤24.00	85.7%	68.4%	0.799	0.001^{**}	0.662-0.937
CRP (mg/dL)	≤4.46	95.2%	42.1%	0.669	0.068^{NS}	0.499-0.840
ALB (g/dL)	5.05	42.9%	89.5%	0.613	0.223^{NS}	0.435-0.791
OSM (pg/ml)	86.21	38.1%	89.5%	0.615	0.213^{NS}	0.437-0.794
CALP (ng/mL)	≤1156.00	95.2%	26.3%	0.497	0.978^{NS}	0.310-0.685
ADA (ng/mL)	≤50.75	42.9%	73.7%	0.531	0.735^{NS}	0.348-0.714
PLT ($*10^3$)	316.50	90.5%	47.7%	0.675	0.058^{NS}	0.508-0.843
Age (year)	≥31.50	71.4%	63.2%	0.711	0.023^{*}	0.549-0.872
BMI (kg/m^2)	≥27.99	38.1%	100%	0.683	0.048^{*}	0.515-0.851

(*) Significant difference (P<0.05), (**) Highly Significant difference (P<0.01).
ADA: anti-drug antibody; **ALB:** albumin; **BMI**; body mass index; **CALP**: calprotectin; **CRP**:C-reactive protein; **ESR**: erythrocyte sedimentation rate; **HGB**: hemoglobin; **MPV**: mean platelet volume; **NS**: No significant differences (P>0.05); **OR**: Odds Ratio; **OSM**: oncastatin-m; **PCV**: packed cell volume; **PLT**: platelet; **PMS**: Partial mayo score.

Discussion

Infliximab was the first anti-TNF biologic agent used in the treatment of UC. It is a chimeric recombinant monoclonal IgG1 that binds with high affinity to human TNF[36]. At the beginning of treatment, infliximab had a good outcome, but over time, some patients fail to respond to the therapy. There are ways to correct this loss of response, such as treatment optimization, addition of immunosuppressant, or switching to another drug class of the biological agents. Optimization can be done empirically or by monitoring TL and detecting ADAs[37-39].The current study involved 40 UC patients on infliximab where TDM was done to determine the infliximab TL and the presence of ADAs to infliximab which can aid in making adjustments to therapy by escalating the dose of infliximab, shorten the interval between doses or switching to another drug class. To the best of our knowledge, this is the first study in Iraq to determine the TL and ADAs to infliximab in UC patients.

Results of the current study showed that, out of 40 patients, 6 patients were in remission and low TL, 1 patient in active disease with low TL and no ADAs (non-immune pharmacokinetics failure), and 3 patients in active disease with low TL and low positive ADAs (immune pharmacokinetics failure). Accordingly, it is recommended that these patients undergo intensification of drug dose or shorten interval between doses[40]. In addition, there were 14 in remission state with achievement of target TL (need to continuation of therapy), 9 patients in active disease with high positive ADAs (need to switch therapy), and 7 patients in active disease despite achieving target TL (need to switch therapy)[40]. A study by Vande Casteele *et al*. in patients with IBD found that 43.7% of the patients on maintenance infliximab therapy had therapeutic TL compared to 52.5% in the current study[25]. Another study in Brazil on 40 patients with CD found that 80% of all patients had TL above the therapeutic concentration, and of these patients, 18 had active disease and 14 were in remission[41].

Also, in the current study, routine blood count (HGB, PCV, MPV, PLT), routine inflammatory marker (ESR, CRP), and albumin were measured and found that only PCV and ESR had difference between patients who achieved target TL and patients not achieved target TL, and only ESR had an association with achievement of TL. Erythrocyte sedimentation rate and CRP are acute phase reactants whose levels rise with inflammation but also with other conditions. Also, CRP may be more sensitive than ESR and correlates better with disease activity in IBD. Both CRP and ESR are sometimes used to track disease activity, but normal ESR and CRP values do not exclude complications of IBD or flares of disease. Compared with CRP, ESR will peak much less rapidly and may also take several days to decrease, even if the clinical condition of the patient or the inflammation is ameliorated. Erythrocyte sedimentation rate is one of component of Truelove and Witts' severity index which provide an objective disease activity assessment that assists clinical decision making in UC patients[42-44]. A study by S. Choi in pediatric IBD found that there was an association between ESR and TL of infliximab and can use a cut-off value of 18 mm/hr to predict the TL of infliximab[45]. Orfanoudakia *et al*. found that only CRP among other biomarkers (ESR, albumin, HGB, PLT) had higher significant difference with TL[46].

Another marker in this study was serum calprotectin, where the current study was the first

study which investigated its association with TL of infliximab in patients with UC. Faecal calprotectin (FC) testing in clinical practice has limitations, as opposed to serum CALP testing. The clinical value of faecal collection may be affected by patient obstacles, sample delivery delays, and processing delays[47]. The best time to sample FC in an active UC is unclear, and shows significant within-day variability. In routine practice, a blood-based biomarker such serum calprotectin (SC) would be more practical and more acceptable to patients[48]. The finding of the current study with respect to SC not favor the use of this marker as a predictor for achievement of the target TL of infliximab (no significant association between them). Regarding OSM, no significant difference between the two groups was found with no significant association between serum OSM and achievement of target TL. According to a recent study, OSM is a promising marker for IBD patient diagnosis and follow-up, but its predictive power for predicting how response to IBD treatment is rather limited[49]. Unexpectedly, Verstockt et al. reported a significantly elevated mucosal OSM gene expression in IBD patients who did not achieve endoscopic remission after starting therapy with an anti-TNF, but the result of the study could not identify any significant correlation between blood OSM concentrations and endoscopic remission[50].

This unexpected result (no significant correlation between blood OSM concentrations and remission) could be attributed to variations in the study design, such as reporting a relative OSM measurement rather than a whole, and timing of the primary outcome assessment. Blood-based OSM concentrations between those who achieved remission and those who did not differed statistically significantly across all studies examining remission (biochemical, mucosal, and clinical) with an anti-TNF at 1-year[51, 52]. It's possible that Verstockt et al.'s evaluation of remission at 6 months was too short[50]. This notion is strengthened by the findings of Minar et al., who found that while anti-TNF-mediated biochemical and clinical remission at 3 months did not correlate with plasma OSM concentrations, while at one year did correlate with plasma OSM concentrations of less than 143.5 pg/mL[52].

Other factors with significant difference between patients achieved the target TL and patient not achieved target TL were age, BMI but only age had association with TL and can predict the target level. The current study found that patients who achieved TL had older age than patients not achieved TL. In 2021, Kantasiripitak *et al.* found that elderly patients attained infliximab exposure and endoscopic remission similarly to nonelderly patients. Therefore, the same infliximab TL target can be used in TDM[53].

Limitations

This study had some limitations that should be mentioned. First, patients were collected from a single center in Iraq. Whether they can represent the total number of UC patients in Iraq on infliximab and to what extent, requires further investigation. Second, the sample size here is relatively small. In future studies, large sample and multicenter studies should be included in other regions of Iraq to show whether the results here can be confirmed in other UC patients. Third, the results of TDM (TL and ADAs) were delayed because the samples were collected from patients and stored for 6 months and then the lab measurement were performed and lead to delay the recommendation of therapy to the physician and patients.

Conclusion

In conclusion, TDM of infliximab to determine the TL and ADAs can explain the possible causes of non-responsiveness to this drug among UC users with subsequent recommendations based on these findings.

Acknowledgment

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Conflicts of Interest

The authors did not disclose any conflicts of interest.

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Ethics Statements

The research proposal describes the goals of the current study and the proposed data collection techniques was administered to the “College of Pharmacy, University of Baghdad” and the approval was obtained from Scientific and Ethical Committee (approval name: RECAUBCP2992021A, date 29-9-2021). Then approval was also obtained from the Iraqi Ministry of Health. While verbal consent was gained from the patients to participate in the study.

Author Contribution

The authors contribution as follows: study conception and design: second authors; data collection: first and third authors; draft manuscript preparation: first and second Author. All authors reviewed the results and approved the final version of the manuscript.

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مراقبة الدواء العلاجية للإنفلاكسيماب في المرضى العراقيين الذين يعانون من التهاب القولون التقرحي المتوسط الى الشديد

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الخلاصة

أمراض الأمعاء الالتهابية هو مصطلح عام لمجموعة من الاضطرابات الالتهابية مجهولة السبب والمزمنة المنتكسة في الجهاز الهضمي. إنفلاكسيماب، وهو جسم مضاد وحيد النسيلة خيميري، هو دواء يستخدم لعلاج عدد من أمراض المناعة الذاتية. مراقبة الأدوية العلاجية هي أداة لاتخاذ القرار السريري تتيح تعديلات نظام الجرعات استنادًا إلى القياسات السريرية والمختبرية، وعادة ما تكون تركيزات الدواء في الدم، للوصول إلى التعرض للأدوية المرتبط بأعلى معدل استجابة ممكن. إن التركيزات المنخفضة للإنفلاكسيماب عند ٣ إلى ٧ ميكروجرام/مل هي الأكثر فعالية في إحداث استجابة لدى المرضى الذين يعانون من مرض التهاب الأمعاء. كانت أهداف الدراسة الحالية هي تحديد مدى تحقيق هدف مستوى العلاج الادنى، وتطوير الأجسام المضادة المضادة للأدوية للإنفلاكسيماب، وتقييم الاستجابة للعلاج ودراسة علاقة مستوى العلاج مع متغيرات مختلفة في المرضى الذين يعانون من التهاب القولون التقرحي. أجريت هذه الدراسة المقطعية في "مستشفى أمراض الجهاز الهضمي والكبد التعليمي / مدينة الطب / بغداد / العراق" خلال الفترة من مايو ٢٠٢٢ إلى نوفمبر ٢٠٢٢. تم تضمين أربعين مريضًا مرشحًا مصابين بالتهاب القولون التقرحي. وفقًا لمستوى العلاج ونشاط المرض وتطور الأجسام المضادة، تمت التوصية بتصعيد الجرعة لـ ١٠ مرضى (٢٥٪)، وأوصى بتبديل العلاج لـ ١٦ مريضًا (٤٠٪)، وأوصى بمواصلة نظام الجرعة نفسه لـ ١٤ مريضًا. (٣٥٪). بالإضافة إلى ذلك، أظهرت نتائج الدراسة الحالية أن العمر ومؤشر كتلة الجسم ونسبة حجم الخلايا الحمراء في الدم كانت أعلى بكثير وكان معدل ترسيب كرات الدم الحمراء أقل بشكل ملحوظ لدى المرضى الذين حققوا مستوى إنفلاكسيماب المستهدف مقارنة بالمرضى الذين لم يحققوا المستوى المستهدف. باستخدام تحليل الانحدار الثنائي متعدد المتغيرات، يمكن فقط استخدام العمر ومعدل ترسيب كرات الدم الحمراء للتنبؤ بتحقيق المستوى الأدنى المستهدف من إنفلاكسيماب. في الختام، مراقبة الأدوية العلاجية للإنفلاكسيماب لتحديد مستوى الأدنى للعلاج والأجسام المضادة للأدوية يمكن أن تفسر الأسباب المحتملة لعدم الاستجابة لهذا الدواء بين مرضى التهاب القولون التقرحي مع توصيات لاحقة بناء على هذه النتائج.

الكلمات المفتاحية: الأجسام المضادة للأدوية، الإنفلاكسيماب، مراقبة الدواء العلاجية، التهاب القولون التقرحي، مستوى الحد الادنى.