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Relationship between Ustekinumab trough concentrations and clinical, biochemical and endoscopic outcomes in Crohn's disease

A multi-center nationwide retrospective study (TARGET STUDY)

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Abstract

Ustekinumab has been shown to be effective in inducing and maintain clinical and endoscopic remission in Crohn disease (CD). We aim to assess whether ustekinumab trough levels are associated with improved outcomes in CD in real-life. We recruited patients with CD who were treated with ustekinumab for at least 6 months from January 2017 to June 2023. Patients received ustekinumab 6 mg/kg intravenous induction followed by 90 mg every 4-, 8-, or 12-weeks during maintenance were included. We assessed clinical, biochemical, and endoscopic outcomes. Trough concentrations of ustekinumab that were taken from week 42 to week 52 were measured. Primary outcome was to evaluate the relationship between ustekinumab trough concentrations and clinical remission, biochemical normalization, and endoscopic remission. Logistic regression was conducted to assess outcomes. A total of 137 patients with CD, median age of 32 years and 83 (60.6%) males. The median serum levels of ustekinumab measured was 7.2 mcg/mL (interquartile range [IQR] 3.1–9.6). Using Spearman correlation analysis, a strong negative correlation was observed between ustekinumab drug levels and simple endoscopic score (SES-CD) ($r = –0.464$, $P < .001$). Additionally, ustekinumab drug levels demonstrated substantial negative correlations with disease severity measured by Harvey-Bradshaw index (HBI) score ($r = –0.582$, $P < .001$), C-Reactive Protein (CRP) levels ($r = –0.598$, $P < .001$) and fecal calprotectin (FC) levels ($r = –0.529$, $P < .001$). A multivariable analysis adjusted for age, sex and body mass index (BMI) showed a significant association between ustekinumab serum drug levels and predefined outcomes. Ustekinumab serum drug level above 4.5 mcg/mL was associated with 24% increase in the likelihood of having an SES-CD score <3 (OR 1.24, confidence interval [CI] 1.12–1.37, P value < .001), 44% more likely to achieve HBI score <5 (OR 1.44, CI 1.26–1.65, P value < .001), 52% higher likelihood of CRP more than 10 (OR 1.52, CI 1.31–1.77, $P < .001$), and 42% increased likelihood of FC more than 250 (OR 1.42, CI 1.24–1.62, $P < .001$). Ustekinumab trough concentrations above 4.5 mcg/mL were associated with clinical, biochemical and endoscopic remission in CD. Prospective data is warranted to confirm these findings.

Abbreviations: Anti-TNF = tumor necrosis factor antagonists, BMI = body mass index, CD = Crohn disease, CI = confidence interval, CRP = C-reactive protein, FC = fecal calprotectin, HBI = Harvey-Bradshaw index, IBD = inflammatory bowel disease, ICD = international classification of diseases, IQR = interquartile range, SES-CD = simple endoscopic score.

Keywords: Crohn, drug levels, healing, remission, Ustekinumab

1. Introduction

Crohn disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by cycles of relapse and remission and requires long-term treatment to control the disease.[1] The complex nature of the disease and unpredictable course renders its management challenging, particularly in patients exhibiting refractory responses to conventional therapies.[1,2]

Patients' consents were waived as it is a retrospective study by the same ethical committee.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Ethical approval for this study was obtained by the standing committee for coordination of health and medical research at the ministry of health of Kuwait (IRB No. 2917/2023) and as per the updated guidelines of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and of the US Federal Policy for the Protection of Human Subjects.

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The advent of biologic medications has markedly altered the management and prognosis of the disease, providing patients with markedly improved quality of life.[3,4] However, many patients with moderate-to-severe CD fail first-line tumor necrosis factor antagonists (anti-TNF) therapies, necessitating an escalation in treatment to effectively control the disease[1,2]

Anti-TNFs are among the first biologics used in the treatment of IBD, however, the primary non-response as well as secondary loss of response pose a challenge and often require switch to a different biologic medication.[1,2] For moderate-to-severe cases, current guidelines suggest starting with vedolizumab or ustekinumab even at an earlier stage of the disease for patients who fail conventional therapy and or anti-TNF to keep the disease in remission.[2] However, surgery was shown to be an effective option and maybe better than biologic therapy in patients with limited ileal CD.[5,6]

Ustekinumab is a fully humanized IgG1 monoclonal antibody that targets the p40 subunit of the interleukin IL-23 and IL-12.[7] It is currently indicated for the management of moderate-to-severe types of the disease and has been shown to successfully induce and maintain remission in the UNITI clinical trials in patients with moderate-to-severe CD.[7,8] The double-blind phase 3 trials, UNITI-1 and UNITI-2 examined the efficacy and safety of induction therapy of ustekinumab in patients with CD who failed anti-TNF therapy (UNITI-1), and in patients on conventional therapy (UNITI-2).[7] The induction trials were placebo-controlled and were done over 8 weeks. Clinical response and remission were significantly higher in the treatment group. Moreover, the response rates in the UNITI-2 trial were numerically higher, indicating that previous failure of an anti-TNF could affect the efficacy of ustekinumab induction response.[7] The safety and efficacy of the maintenance dose of ustekinumab were then examined in the IM-UNITI trial, which is an extension of the UNITI-1 and UNITI-2 trials.[7,8] Patients who have successfully completed the induction therapy were assigned to the IM-UNITI for the efficacy of the maintenance dose in inducing remission. Both the 44-week maintenance trial, as well as the 4-year LTE trial, demonstrated a significant clinical response and remission while maintaining an acceptable safety profile.

Therapeutic drug monitoring has an important role in the succession of the biologic therapy.[9,10] Low drug levels have been consistently linked to the development of anti-drug antibodies as well as secondary loss of response and treatment failure.[1] Target therapeutic levels of ustekinumab have been outlined in existing literature, however, their impact on treatment outcomes remains inadequately explored.[11,12] The aim of this study is to investigate the association between ustekinumab trough level and effectiveness outcome including biochemical, clinical and endoscopic remission in patients with CD.

2. Methods

This study was performed and reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13] Adults with moderate-to-severe patients with CD who were biologic experienced or naïve were assessed. Patients initiating or already being treated with ustekinumab were recruited from January 2017 to June 2023 at 7 governmental hospitals in Kuwait (Mubarak al-Kabeer Hospital, Alsabah Hospital, Alamiri Hospital, Aladan Hospital, Jahra Hospital, Farwaniya Hospital, and Kuwait Oil Company Hospital).

A retrospective chart review of patients already on ustekinumab between 42 to 52 weeks after initiation of therapy, at a one-time visit, and had clinical [the Harvey-Bradshaw index (HBI)] and biomarker [C-reactive protein (CRP) and fecal calprotectin (FC)] assessment completed. Baseline (prior to treatment) and post-treatment clinical, biomarker and endoscopic data were extracted from electronic medical records. Patients received ustekinumab 6 mg/kg intravenous induction followed by 90 mg every 4-, 8-, or 12-weeks during maintenance for CD were included. Blood samples were collected for ustekinumab trough levels within 24 hours of the next maintenance dose. Exclusion criteria included: Pregnant patients, age < 18, patients with missing outcome data, and patients whose colonoscopic examination of the terminal ileum was not assessed.

Ustekinumab drug trough concentrations were analyzed using a drug-tolerant liquid phase homogeneous mobility shift assay (HMSA, Prometheus Laboratories Inc., San Diego, CA).

Diagnosis of IBD was made according to the international classification of diseases (ICD-11 version: 2019/21). Patients were considered to have IBD when they had ICD-11 DD70, DD70.1, DD70.2, DD70.3, DD70.4, DD70.5, DD70.6 corresponding to CD.[14]

Ethical approval for this study was obtained by the standing committee for coordination of health and medical research at the Ministry of Health of Kuwait (IRB No. 2917/2023) and as per the updated guidelines of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and of the US Federal Policy for the Protection of Human Subjects. Patients' consents were waived.

Primary analysis evaluated the relationship of ustekinumab drug concentrations (above and below 4.5 μg/mL) with clinical outcomes (clinical remission; HBI < 5, biomarker normalization (CRP < 5mg/L and FC < 200 μg/g) and endoscopic remission using the simple endoscopic score (SES-CD) ≤ 2. One blinded reviewer (FA) jointly with an IBD endoscopist (MS) calculated SES-CD scores retrospectively, using endoscopy reports and images. Ustekinumab drug concentration cutoff was based on a recent systematic review and meta-analysis where most studies used 4.5 μg/mL as a cutoff value to measure response rate.[9]

2.1. Statistical analysis

Analyses were conducted using SPSS Statistics package (Version 29.0. Armonk, NY: IBM Corp.). Descriptive statistics were calculated to express frequencies and proportions of categorical variables, expressed as means with standard deviation (SD), median with interquartile range (IQR) and percentages. Spearman correlation coefficients (r) were deployed to assess the relationships between ustekinumab drug levels and the continuous variables. Logistic regression was conducted to investigate the association between ustekinumab therapeutic drug level and SES-CD, HBI, CRP, and FC levels. All analyses were controlled for age, sex and body mass index (BMI). The results of the logistic regression were presented as odds ratios (OR) with a null value of "1." Statistical significance was set to a P value < .05 and confidence interval (CI) of 95% for all associations.

3. Results

A total of 137 patients with CD, were included in the cohort with median age of 32 (IQR 24.5–41) years and 83 (60.6%) males (Fig. 1). 128 (93.4%) of patients were of Middle Eastern ethnicity. The mean BMI kg/m^2 was 24.2 and 31 (22.6%) were smokers. The median serum level of ustekinumab measured was 7.2 mcg/mL (IQR 3.1–9.6). Demographic characteristics of the included cohort are shown in Table 1.

A multivariable analysis adjusted for age, sex and BMI showed a significant association between ustekinumab serum drug levels and SES-CD score. Ustekinumab serum drug level above 4.5 μg/mL was associated with 24% increase in the likelihood of having an SES-CD score <3 (OR = 1.24, 95% CI 1.12–1.37, P value < .001). Similarly, patients with ustekinumab serum drug level above 4.5 are 44% more likely to achieve HBI score <5 (OR = 1.44, 95% CI 1.26–1.65, P value < .001, figure 4). Moreover, the results of the logistic regression analyses (supplementary table 1, http://links.lww.com/MD/N117)

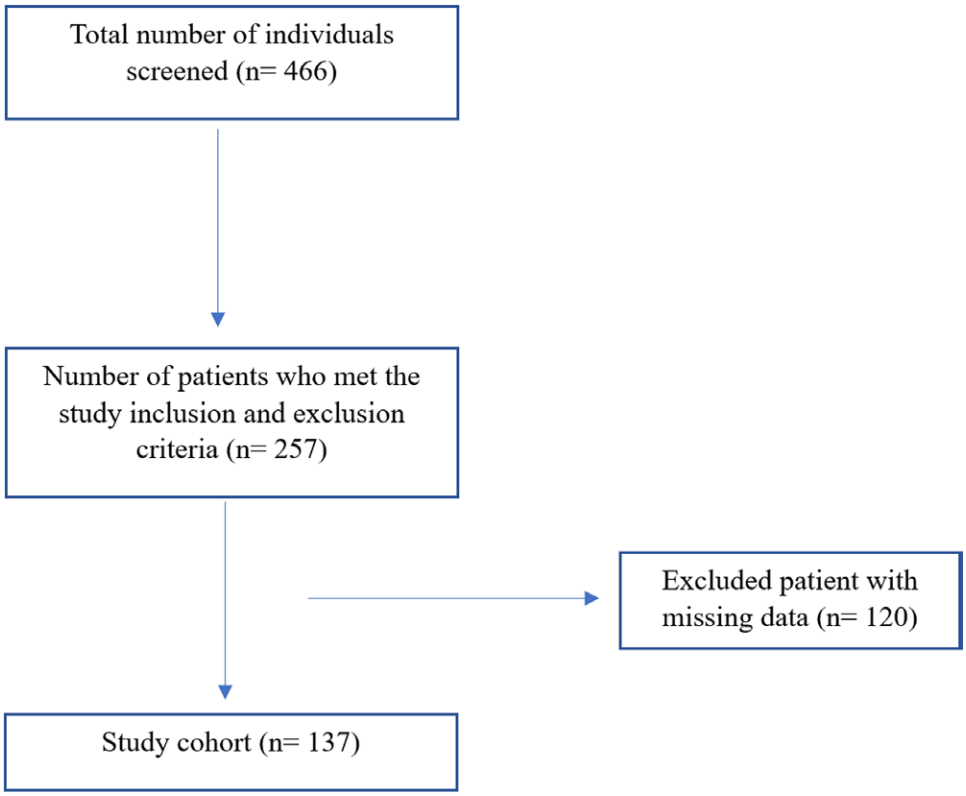

Figure 1. Study enrollment flow chart.

Table 1

Baseline characteristics of the entire cohort.

Variables	Total, N = 137
Age (yr), median (IQR)	32 (24.5–41)
Sex, n (%)	
Male	83 (60.6)
Female	54 (39.4)
Ethnicity, n (%)	
Middle-Eastern	128 (93.4)
Others	9 (6.6)
Smokers, n (%)	31 (22.6)
BMI (kg/m^2), median (IQR)	24.2 (21.2–27.9)
Disease location, n (%)	
L1: ileal CD	63 (46)
L2: colonic CD	12 (9)
L3: ileocolonic CD	55 (40)
L4: upper gastrointestinal CD	7 (5)
Disease behavior, n (%)	
B1: non-stricturing, non-penetrating CD	64 (47)
B2: stricturing CD	36 (26)
B3: penetrating CD	37 (27)
C-reactive protein (CRP), median (IQR)	7.3 (4.5–55.5)
Fecal Calprotectin, median (IQR)	240 (142–396)
SES-CD ≥ 3, n (%)	74 (54.0)
Harvey-Bradshaw Index (HBI) ≥ 5, n (%)	59 (43.1)
Current corticosteroids use, n (%)	16 (11.6)
Current immunomodulators use, n (%)	9 (6.6)
Previous biologics use, n (%)	69 (50.4)
Duration of previous biologics use (mean) in months	13

BMI = body mass index, CD-SES = simple endoscopic score for Crohn disease, HBI = Harvey-Bradshaw index, IQR = interquartile range, n = number, SD = standard deviation.

indicate significant associations between ustekinumab therapeutic drug levels and inflammatory markers. Specifically, individuals with drug levels exceeding 4.5 demonstrated a 52% higher likelihood of having CRP levels <10 mg/L, as evidenced by the odds ratio of 1.52 (95% CI 1.31–1.77, $P < .001$). Similarly, there was a 42% increased likelihood of having low FC levels of <250 mcg/mg among individuals with drug levels above the 4.5 threshold, reflected in the odds ratio of 1.42 (95% CI 1.24–1.62, $P < .001$). The association between ustekinumab and each of the outcomes is illustrated in the forest plot (Fig. 2).

Spearman correlation analysis results are shown in supplementary table 2, http://links.lww.com/MD/N118. The analysis showed that higher ustekinumab serum levels were significantly associated with lower SES-CD scores (r = –0.483, $P < .001$). Additionally, ustekinumab drug levels demonstrated substantial negative correlations with disease severity measured by HBI (r = –0.676, $P < .001$). Figures 3 and 4 show graphical relationship between ustekinumab drug levels and SES-CD scores as well as HBI. Furthermore, ustekinumab drug levels demonstrated significant negative association with inflammatory markers including CRP (r = -783, $P < .001$) and FC levels (r = –0.690, $P < .001$). Finally, there were no statistically significant differences between patients who were biologic naïve vs biologic experienced in all reported outcomes, CRP $P = .25$, FC $P = .11$, HBI $P = .58$, SES-CD $P = .52$.

4. Discussion

In this retrospective cohort study, we aimed to assess the efficacy of ustekinumab trough levels in sustaining biochemical, clinical and endoscopic remission in patients with CD. We found that higher ustekinumab serum levels were significantly associated with lower SES-CD scores. Additionally, ustekinumab drug levels demonstrated substantial negative correlations with disease severity measured by HBI.

Similarly, in a real-life study of 62 patients with CD who were either refractory or intolerant to TNF, patients with endoscopic response to treatment had a higher mean ustekinumab serum

level than those without endoscopic response [4.7 µg/mL vs 3.8 µg/mL, $P = .03$]. Additionally, patients with high ustekinumab serum drug concentrations [>4.7 µg/mL] had higher endoscopic response rates at week 26 and lower CRP concentrations than patients with lower drug levels.[15]

Another real-life study analyzed ustekinumab serum trough levels and antibody titers in 47 patients with CD on maintenance therapy. The study found that regardless of prior biologic exposure, higher ustekinumab serum trough levels were significantly associated with a higher rate of achieving mucosal healing and mucosal response in patients with CD.[16]

In our study, we found that individuals with drug levels exceeding 4.5 demonstrated a 52% higher likelihood of having CRP levels <10 mg/L. Interestingly, one study aimed to identify the optimal ustekinumab trough levels predicting clinical, laboratory and endoscopic remission in CD patients. The study concluded that attainment of endoscopic remission requires higher ustekinumab trough levels than required for normalization of CRP and serum albumin levels. However, the study was limited by limited by small sample size (28 patients).[17]

Additionally, we found that there was a 42% increased likelihood of having low FC levels of <250 mcg/mg among individuals with drug levels above the 4.5 threshold. A study conducted in the Netherlands, investigated the association between ustekinumab serum trough levels and biochemical remission defined as CRP ≤ 5 mg/L and/ or FC ≤ 250 mg/kg. Authors found that patients achieving biochemical remission at weeks 12 and 24 had significantly higher ustekinumab levels at week 8 compared to patients without biochemical remission.[18]

It is important to emphasize that there is uncertainty surrounding the established therapeutic range for ustekinumab. This uncertainty is reflected by the differences in reporting levels and cutoffs in published literature.[19] Further refining of the target ustekinumab trough concentration is essential to evaluate the need for achieving higher levels, particularly in patients who have not responded to standard dosing.

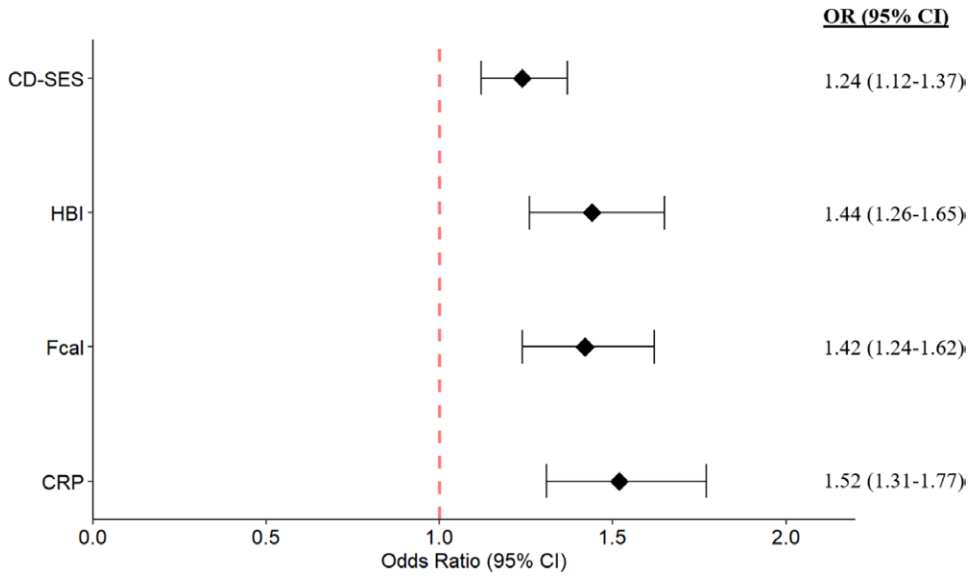

Figure 2. Forest plot illustrating the association of ustekinumab therapeutic serum drug level, CD-SES score, HBI score, and inflammatory markers (CRP and fecal calprotectin [FC]). CD-SES = simple endoscopic score for Crohn disease, HBI = Harvey-Bradshaw index.

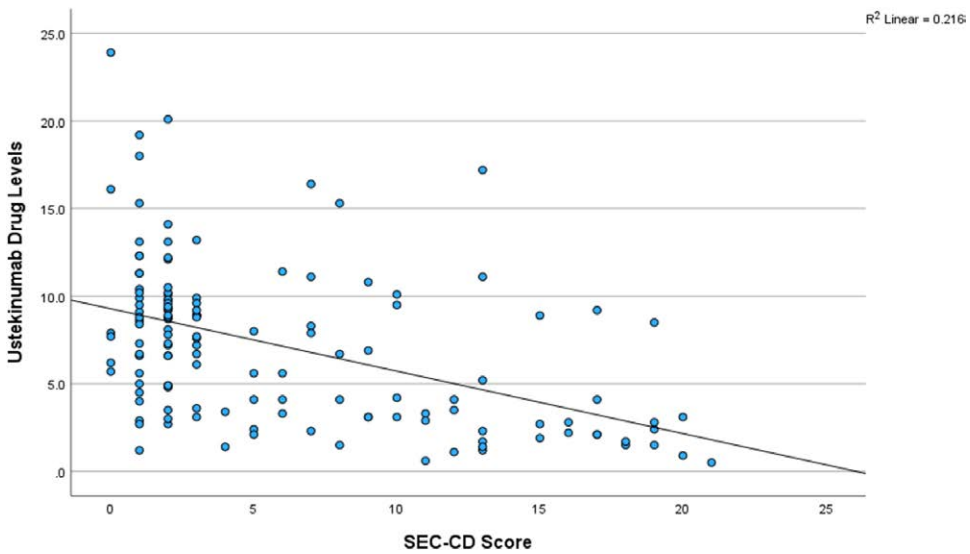

Figure 3. Spearman correlation coefficients (r) showing the relationship between ustekinumab drug levels and simple endoscopic score (SES-CD).

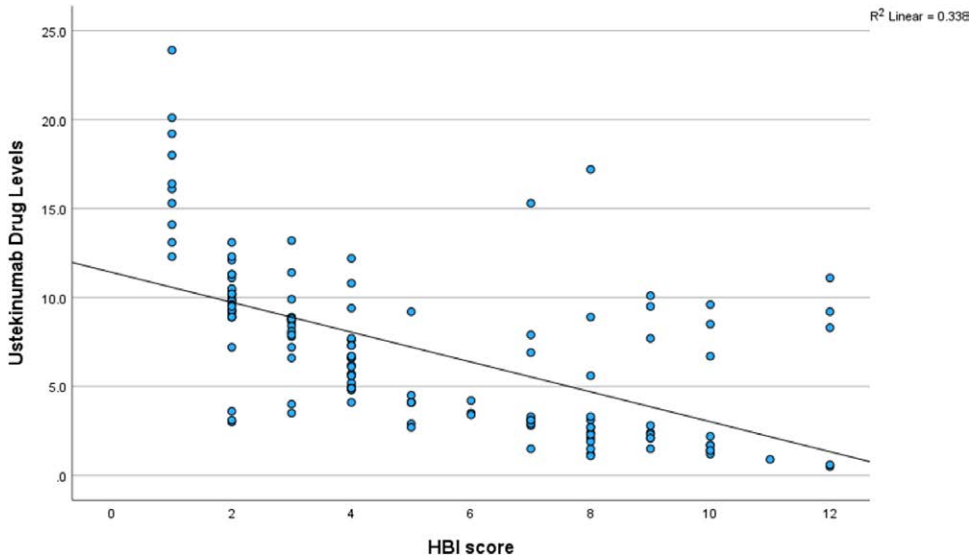

Figure 4. Spearman correlation coefficients (r) show the relationship between ustekinumab drug levels and Harvey-Bradshaw index (HBI).

This research holds significant clinical implications. It adds valuable insights to the existing body of literature regarding the potential significance of serum ustekinumab levels in the broader landscape of therapeutic drug monitoring. These findings can inform personalized treatment approaches with biologics for patients. The observed correlation between serum ustekinumab levels and mucosal healing, especially in CD, suggests that proactively monitoring therapeutic drug levels may be beneficial. This approach could help assess whether the prescribed dosage regimens are optimal, thereby enhancing the chances of achieving a mucosal response.

This is the first multi-center study in Middle East to describe the relationship of ustekinumab drug trough concentrations with clinical, biochemical and endoscopic outcomes in CD. We included all important treatment target outcomes that are important to prevent complications and maintain remission. Additionally, we had strict inclusion and exclusion criteria to minimize bias and confounders.

However, our study has some limitations. The retrospective nature of this study is not designed to measure causations and can only be used to investigate for possible associations Additionally, the retrospective design may lead to bias such as the potential effect of other medications such as corticosteroids or immunomodulators, although there were low in numbers. Finally, we had to rely on data reported in the electronic patient file.

5. Conclusion

The findings of this study suggest a strong possible relationship between higher drug levels and achieving clinical and endoscopic remission expressed as HBI, CD-SES, respectively, and toward lower inflammatory markers. That in return, emphasizes the importance of monitoring drug levels in individuals to potentially mitigate inflammatory responses and achieve clinical as well as endoscopic remission. The statistical significance of these results underscores the robustness of these associations, highlighting their relevance and importance in clinical contexts.

Author contributions

Conceptualization: Mohammad Shehab.
Data curation: Mohammad Shehab.
Formal analysis: Israa Abdullah.
Methodology: Mohammad Shehab.
Supervision: Fatema Alrashed.
Writing – original draft: Mohammad Shehab, Israa Abdullah, Ahmad Alfadhli.
Writing – review & editing: Ahmad Alfadhli, Fatema Alrashed.

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