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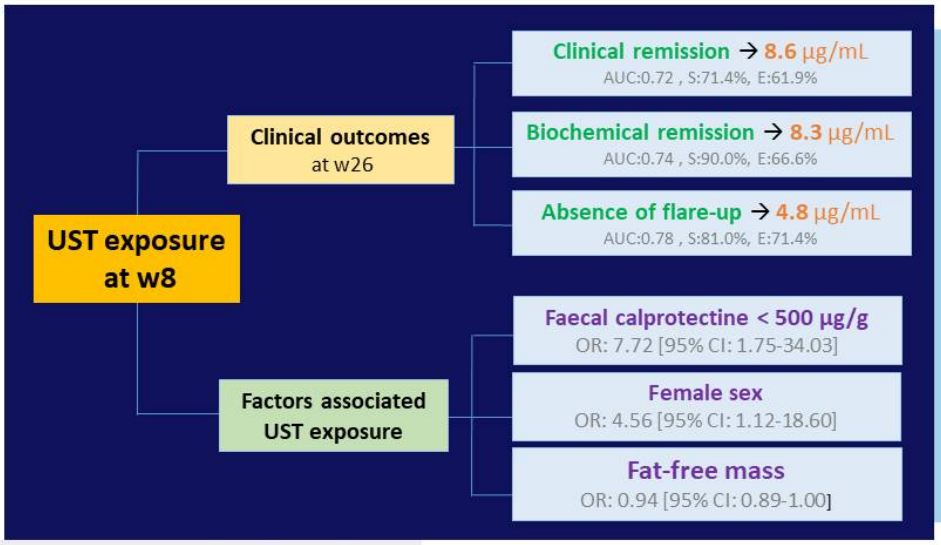

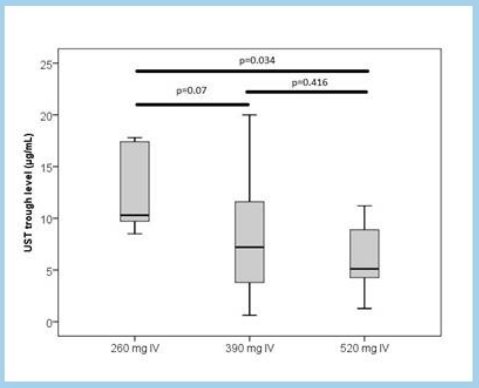

Figure. Relationship between UST trough level and dose induction

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Impact of ustekinumab exposure on clinical outcomes during induction in inflammatory bowel disease

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Keywords: Ustekinumab. Inflammatory bowel disease. Pharmacokinetics. Induction. Trough levels. Therapeutic drug monitoring.

Abbreviations

AUC: area under the curve

BMI: body mass index

CD: Crohn's disease

CRP: C-reactive protein

FCP: faecal calprotectin

FFM: Fat-free mass

IBD: inflammatory bowel disease

IQR: interquartile ranges

UTL: ustekinumab trough levels

SD: standard deviation

TDM: therapeutic drug monitoring

UC: ulcerative colitis

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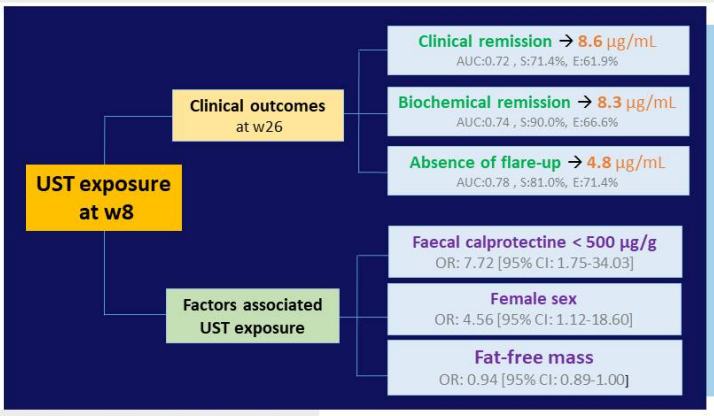

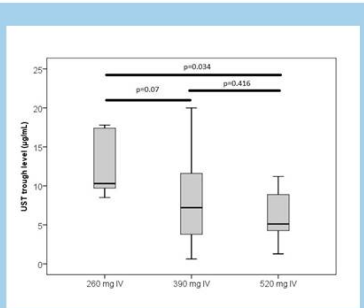

Figure. Relationship between UST trough level and dose induction

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Abstract

Background

Understanding the relationship between ustekinumab (UST) exposure and clinical outcomes in inflammatory bowel disease (IBD) induction is crucial. However, evidence remains limited, highlighting the need to comprehend UST's pharmacokinetic variability for tailored treatments.

Aims

This study aimed to investigate the association between UST exposure during the induction phase and clinical outcomes and identifying factors associated with UST exposure during this period.

Methods

A retrospective observational study was conducted on a cohort of consecutive IBD patients. The primary endpoint was to assess the association between UST exposure at week 8 and both clinical and biochemical remission at week 26, as well as the absence of disease flare-ups during the initial six months of treatment. The secondary endpoint was to investigate the relationship between baseline characteristics and UST exposure at week 8.

Results

A total of 56 IBD patients were included. Variables associated with adequate UST exposure included baseline fecal calprotectin < 500 µg/g (OR: 7.72 [95% CI: 1.75-34.03]) and female sex (OR: 4.56 [95% CI: 1.12-18.60]). A cut-off UST trough levels of 8.3 µg/mL yielded an area under the curve (AUC) of 0.74 (95% CI: 0.58-0.90, p=0.021) to predict normal fecal calprotectin levels, and 8.6 µg/ml resulted in an AUC of 0.724 (95% CI: 0.558-0.863) to predict clinical remission.

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Conclusions

This study demonstrates a significant association between UST concentrations and clinical and biochemical remission in IBD patients. Results suggest that standard induction doses may not be sufficient for all patients, highlighting the importance of treatment individualization to optimize outcomes.

Lay summary

This research addressed the impact of ustekinumab exposure on patients with inflammatory bowel disease (IBD) during the first six months of treatment, also exploring pharmacokinetic variability. Significant variability in ustekinumab levels was observed, linked to differences in clinical and biochemical remission, as well as in flare prevention. Higher ustekinumab levels at week 8 consistently correlated with better clinical outcomes by week 26, suggesting a potential therapeutic target for optimizing ustekinumab dosing in IBD patients. This supports the need to consider treatment individualization and monitoring ustekinumab concentrations, as standard doses may not be suitable for all patients, especially those with higher risk profiles. These findings underline the importance of personalized care to optimize clinical outcomes in IBD.

Authorship

CIN: conception and design of the study, acquisition, analysis and interpretation of data, drafting of the article and review and final approval of the version.

MRS and LRR: acquisition, conception and design of the study, drafting of the article and review and final approval of the version.

INP: acquisition, analysis and interpretation of data, writing of the article, and final approval of the version.

RGE: acquisition, analysis and interpretation of data, writing of the article, and final approval of the version.

EUS: conception and design of the study, drafting of the article and review and final approval of the version.

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Key points

- Significant association between UST concentrations and clinical and biochemical remission in patients with IBD.
- Standard induction doses may be insufficient, particularly in higher-risk patient subgroups.
- Need for treatment individualization and monitoring of UST concentrations to optimize clinical outcomes in IBD patients

Conflicts of interest

The authors declare no conflict of interests

Statement of Generative AI and AI-assisted technologies in the writing process

To optimize the accuracy and style of my manuscript, I have utilized the capabilities of ChatGPT-4.0, an artificial intelligence language model developed by OpenAI. This tool has allowed me to receive suggestions and guidance on the structure, writing, and coherence of my scientific text. It is important to mention that, although I have used ChatGPT-4.0 as an assistant, all the content and ideas presented in the manuscript are the result of my own research and knowledge.

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), presents as a complex and chronic inflammatory condition affecting the gastrointestinal tract[1,2]. Despite advancements in therapeutic options, achieving and sustaining clinical remission remains challenging for many patients. Ustekinumab (UST) is a monoclonal antibody that binds to the p40 subunit of interleukin(IL)-12 and IL-23 and thereby inhibits its bioactivity[3,4].The efficacy and safety of UST in moderate to

severely active CD[5,6] and UC[7] was investigated in phase 3 placebo-controlled studies. UST is administered as an intravenous loading dose based on weight, followed by a fixed subcutaneous dose of 90 mg every 8 or 12 weeks.

In recent years, substantial evidence has emerged supporting therapeutic drug monitoring (TDM), allowing for dose individualization to attain better exposure and optimize therapeutic outcomes[8-10]. However, there is a significant knowledge gap regarding the role of TDM in the context of UST. Reactive TDM is widely accepted[9,10] , while the positioning of the proactive strategy in the clinical guidelines of the European Crohn's and Colitis Organisation (ECCO)[11] and American College of Gastroenterology (AGA)[12] is not routinely recommended. Nonetheless, experts[8-10,13,14] suggest that the proactive approach could be particularly beneficial during the induction phase of UST treatment.

Understanding the relationship between UST exposure and clinical outcomes is critical during the induction phase to optimize therapeutic strategies. Despite the importance of this association, current evidence remains limited. Additionally, elucidating the pharmacokinetic variability of UST during the induction phase is essential for tailoring treatment approaches to individual patient profiles. In this context, it is imperative to investigate the prevalence of suboptimal UST levels and to identify which patients, based on clinical and demographic factors, may benefit from proactive TDM to optimize outcomes.

The primary objective of this study was to investigate the relationship between UST exposure during the induction phase and clinical outcomes within the first six months of treatment. Secondary objectives included exploring the pharmacokinetic variability of UST trough levels (UTL) during induction and identifying factors associated with its exposure during this period.

Methods

Study design and patient cohort

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A retrospective observational study was conducted on a cohort of consecutive IBD patients at a single center within a regional reference hospital in Murcia, southeastern Spain. The study encompassed adult patients (>18 years) diagnosed with CD and UC who initiated UST treatment between January 2018 and June 2023. Eligible patients were those who received the standard induction regimen of UST infusion at 6 mg/kg at week 0, followed by a subcutaneous dose of 90 mg at week 8. Patients lacking UTL during the induction period (week 8) or those with missing information regarding their clinical responses or laboratory parameters were excluded from the study. The research was approved by the local Ethical Research Committee

Data Collection

The following demographic and clinical data were collected: sex, age, weight, body mass index (BMI), fat-free mass (FFM), diagnosis, disease behaviour and location according to the Montreal Classification at the time of diagnosis. Additionally, data on perianal disease, previous surgery related to the disease, history of biological and steroidal therapy, the use of concomitant immunosuppressive therapy, and biochemical parameters including albumin, C-reactive protein (CRP), faecal calprotectin (FCP), and haemoglobin were recorded. FFM determined using the Janmahasatian model[15].

Serum ustekinumab levels and pharmacokinetics parameters

UTL were measured at week 8 of the induction phase, just before the next subcutaneous dose (trough level). Both trough levels and the presence of anti-UST antibodies were determined using a validated enzyme-linked immunosorbent assay (ELISA) kit (ProMonitor®; Grifols, Spain).

The pharmacokinetic parameters assessed included clearance (CL), expressed in liters per day ($L \cdot day^{-1}$), central volume of distribution (Vc) and peripheral volume of distribution (Vp), both expressed in liters (L), half-life, expressed in days, the elimination rate constant (Ke), expressed in per day (day^{-1}), and area under the

concentration-time curve (AUC), expressed in µg·day/mL. These parameters were calculated based on serum trough levels.

A Bayesian prediction with NONMEM software (version 7.5.0; Icon Development Solutions Ellicott City, MD, USA) based on the population pharmacokinetic model developed by Aguiar et al[16] was used to determine the individual pharmacokinetic parameters of each patient. This model is described as a two-compartment extravascular model with first-order elimination and absorption. To estimate pharmacokinetic parameters after administering the intravenous induction dose, the model was adapted to reflect two-compartment intravascular kinetics.

Endpoints

Disease severity was assessed using the Harvey-Bradshaw Index (HBI) for CD and the Partial Mayo Score (PMS) for UC. Clinical remission was defined as an HBI score of less than 5 for CD and a PMS of 0-1 for UC. Biochemical remission was defined as a FCP< 50 µg/g in faeces. Additionally, the cut-off point for FCP < 150 µg/g was calculated to further evaluate therapeutic response. Flare-ups during the first six months of treatment were also assessed, characterized by an increase in UST dosage, use of systemic corticosteroids, hospitalization, or surgery related to the disease.

The primary endpoint was to assess the association between UST exposure at week 8 and both clinical and biochemical remission at week 26, as well as the absence of disease flare-ups during the initial six months of treatment. The secondary endpoint was to investigate the relationship between baseline characteristics and UST exposure at week 8.

Statistical analysis

Categorical data are shown as absolute numbers and percentages, whereas continuous variables are expressed as median values and measures of variability as interquartile ranges (IQR). Continuous variables were tested using the Mann-Whitney U test or Kruskal-Wallis and categorical variables were analyzed using the Fisher's exact test. Receiver operating characteristic (ROC) curves were used to estimate the cut-off of the

UST trough concentration. The best cut-off value was generated according to the maximal value of sensitivity plus specificity. Univariate regression analysis was performed to identify factors associated with achieving optimal UTL at week 8. A p value of < 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS for Windows (version 23.0; SPSS Inc., Chicago, IL, USA).

Results

Study population characteristics

A total of 56 patients with in IBD were included in this study, of which 55.7% were men. The mean age at the start of treatment was 48.6 years (SD: 17.0). The majority of patients (80.4%) were diagnosed with CD, while the remaining 19.6% had UC. Among the additional characteristics of the cohort, 17.9% presented with extraintestinal manifestations and 22.2% had undergone previous surgery related to their IBD. The majority of patients exhibited significant disease severity at the initiation of UST treatment, with 53.6% experiencing moderate disease activity and 26.8% presenting with severe disease activity. Baseline demographics of the study population are summarized in table 1.

The majority of patients (91.1%) had been previously treated with an anti-TNF drug. At the start of the treatment with UST, 16.1% of the patients were concurrently receiving systemic corticosteroids. All patients received their first dose of UST intravenously at 6 mg/kg of body weight, with 67.9% administered 390 mg (55-85Kg), 23.2% administered 520 mg (>85Kg), and the remaining 8.9% receiving 260 mg (<55 Kg).

Pharmacokinetic variability of ustekinumab at week 8

The median UTL at week 8 during the induction period was 7.8 µg/mL (IQR: 7.3), with no UST antibodies detected. Stratification by baseline disease severity showed that patients with mild disease had a median UTL of 11.6 µg/mL (IQR: 9.8), significantly higher than those with moderate disease at 6.7 µg/mL (IQR: 6.5) and severe disease at

4.3 µg/mL (IQR: 7.0) (p=0.013). Median UTL varied by induction dose: 10.3 µg/mL (260 mg) and 5.1 µg/mL (520 mg) (p=0.034) (Figure 1). Weak inverse relationships were noted between UTL at week 8 and body weight (R=-0.421, p=0.001), FFM (R=-0.457, p<0.001), and baseline FCP (R=-0.293, p=0.048) (Table 2). Additionally, female patients showed a median UTL of 10.0 µg/mL (IQR: 5.7), while male patients had a median of 5.2 µg/mL (IQR: 6.5) (p < 0.001).

Multivariable logistic regression revealed associations with achieving UST exposure (>8 µg/mL), including baseline FCP < 500 µg/g (OR: 7.72 [95% CI: 1.75-34.03]) and female sex (OR: 4.56 [95% CI: 1.12-18.60]). FFM showed borderline significance (OR: 0.94 [95% CI: 0.89-1.00]). The significant difference in FFM between men (78.0 kg, SD: 11.5) and women (68.1 kg, SD: 17.3) (p = 0.012) suggests potential confounding of sex by FFM differences.

At week 8, pharmacokinetic analysis revealed median population estimates for clearance at 0.55 $L \cdot day^{-1}$ (IQR: 0.22), for the elimination rate at 0.11 day^{-1} (IQR: 0.03), and for the elimination half-life at 6.19 days (IQR: 1.89). Notably, differences in clearance rates were observed between men and women, with men showing a clearance rate of 0.62 $L \cdot day^{-1}$ and women 0.44 $L \cdot day^{-1}$ (p=0.001), respectively. Additionally, an inverse association was observed between clearance and anthropometric variables such as weight, BMI, and FFM (table 2). Furthermore, no significant differences were observed in any pharmacokinetic parameter between patients with CD and UC (Table 3).

Association of UTL at week 8 with early clinical outcomes

Figure 2 shows the proportions of patients achieving efficacy outcomes at week 26, stratified by UTL during the induction phase. At week 26, 21.7% of the patients (10 out of 46) had FCP levels below 50 µg/g. The median UTL at week 8 was 10.1 µg/mL (IQR: 4.3) for patients with FCP below 50 µg/g, compared to 5.6 µg/mL (IQR: 6.8) for patients with FCP above 50 µg/g (p=0.002). A cut-off UTL of 8.3 µg/mL yielded the highest area under the curve (AUC) of 0.74 (95% CI: 0.58-0.90, p=0.021) to predict a normal FCP levels. This cut-off level demonstrated a sensitivity of 90.0% and a specificity of 66.6%,

indicating a strong predictive value of UTL for assessing the resolution of intestinal inflammation as indicated by FCP levels. Additionally, for FCP levels below 150 µg/g, a cut-off UST trough level of 8.3 µg/mL yielded an AUC of 0.669 (95% CI: 0.54-0.858, p=0.023), with a sensitivity of 73.7% and a specificity of 74.1%.

During the first six months, 25% of the patients (14 out of 56) experienced at least one flare-up. The median UTL at week 8 for those without a flare-up was 9.0 µg/mL (IQR: 7.0), and for those with a flare-up, it was 3.4 µg/mL (IQR: 6.2). The AUC was 0.78 (95% CI: 0.628-0.936, p=0.002) with a cut-off of 4.8 µg/mL at week 8, showing a sensitivity of 81.0% and a specificity of 71.4%.

At week 26, 25.0% (14 out of 56) of patients were in clinical remission. The median UTL in patients in remission was 11.2 µg/ml (IQR: 6.0) compared to 5.9 µg/ml (IQR: 6.7) in those not in remission (p=0.012). A cut-off UTL of 8.6 µg/ml resulted in an AUC of 0.724 (95% CI: 0.558-0.863), with a sensitivity of 71.4% and a specificity of 61.9%.

For the subgroup of patients with Crohn's disease, a separate analysis of ustekinumab levels was performed. The cut-off for clinical remission was 9.4 µg/mL (AUC: 0.759, 95% CI: 0.611-0.908, p=0.010) with a sensitivity of 81.8% and a specificity of 70.6%. For FCP levels <50 µg/g, the cut-off was 8.06 µg/mL (AUC: 0.752, 95% CI: 0.578-0.927, p=0.032) with a sensitivity of 87.5% and a specificity of 67.9%. The absence of flare-ups had a cut-off of 4.62 µg/mL (AUC: 0.788, 95% CI: 0.628-0.948, p=0.03) with a sensitivity of 78.8% and a specificity of 75.0%. No cut-off point was obtained for the subgroup of patients with UC.

Discussion

This study aimed to investigate the impact of UST exposure during the induction phase on clinical outcomes within the first six months of treatment and to explore pharmacokinetic variability. Significant variability in UTL was associated with differences in clinical and biochemical remission, as well as disease flare prevention. Higher UTL at week 8 consistently correlated with better clinical outcomes at week 26,

suggesting a potential therapeutic target for optimizing UST dosing in IBD patients.

UST's pharmacokinetic variability during the induction period suggests differences based on disease severity and body composition. Our findings align with post hoc analyses of pivotal CD[17] (UNITI-I and UNITI-II) and UC[18] (UNIFI) trials, which observed associations with inflammatory burden, disease severity, and hypoalbuminemia. In our study, we did not observe an association with hypoalbuminemia, a condition often present in severe disease flares at onset, likely because none of our patients exhibited it. Although prior studies[19,20] did not find an association with body weight, our research revealed a significant correlation with body weight and FFM. Notably, in patients weighing over 85 kg, despite receiving a higher dose (520 mg) compared to those under 55 kg (260 mg), UST concentrations were lower (5.1 µg/mL compared to 10.3 µg/mL, respectively). Similarly to the findings of Verstock et al.[21], our study also observed an association with female gender. In line with this, the study by Lorenzo González et al.[22] identified female sex as a significant predictor of corticosteroid-free clinical remission at 6 months in CD patients treated with UST. However, it's important to note that this could be attributed to the significant difference in weight between men and women.

Although UST levels were measured at week 8 in our study, earlier determinations may be advantageous in high-risk patients. An earlier evaluation, at week 2 or 4, could identify patients with low exposure following the induction dose and guide the decision to advance the first subcutaneous dose. This approach could optimize therapeutic exposure and improve clinical outcomes in patients who demonstrate suboptimal pharmacokinetic profiles early in the treatment course.

In our study, individual pharmacokinetic parameters were estimated using a previously published model, which was modified to assume a bicompartimental intravenous model. The estimated half-life was 6.1 days, which was lower than that found in other published studies[16-18,23,24]. This difference could be attributed to the fact that unlike our study, those studies were conducted in the maintenance phase.

Previously published studies[17-19,21,25-28] support the association between serum concentrations at week 8 of induction and favourable clinical outcomes. However, the

optimal cutoff point for these results remains undetermined due to outcome variations (e.g., clinical or biochemical remission, mucosal healing), assay differences in UST concentration determination, sampling times, and potential disparities in disease pattern and location. In our study, UTL induction cut-off levels for clinical and biochemical remission were 8.6 µg/mL and 8.3 µg/mL, respectively. We initially used a cut-off point of 50 µg/g for FCP, a more stringent value generally associated with endoscopic remission. However, after performing calculations using a cut-off point of 150 µg/g, no significant differences were observed in clinical outcomes. For the objective of absence of flares, the cut-off was 4.8 µg/mL. These findings align with previous research, such as that conducted by Verstock et al.[21], in a prospective study showing an association between ustekinumab concentrations and clinical remission, setting the cut-off point at 7.2 µg/mL. Similarly, in the study by Alsoud et al.[26], a robust correlation was identified between serum ustekinumab exposure and histological and endoscopic outcomes, with a cut-off point of 8.4 µg/mL. Finally, Hanzel et al.[29] demonstrated a significant correlation between week 8 UST levels and achieving biochemical remission (defined as FCP <100 µg/g) at week 24, identifying an optimal cut-off point of 6.85 µg/mL. Additionally, peak UST levels exceeding 111 µg/mL were associated with endoscopic remission at week 24.

The present study has several limitations that should be considered when interpreting the results. Firstly, the study design was retrospective, which may have introduced biases and limitations inherent to this type of design. Secondly, the sample size utilized was relatively small, which could impact the generalizability of the results and has not allowed for differentiation in cut-off points or estimated pharmacokinetic parameters between patients with CD and UC. The concomitant use of corticosteroids in 16.1% of patients may have influenced the assessment of response and UST levels at week 8; however, the small size of this subgroup (9 patients) limited the ability to conduct a statistically robust analysis. Thirdly, the lack of information regarding endoscopic data in many patients did not allow for an adequate evaluation of the impact of induction UST exposure on endoscopic response.

To our knowledge, there are few studies specifically addressing the relationship between ustekinumab exposure during the induction phase and clinical outcomes in IBD patients. In this context, one of the strengths of our study lies in its focus on filling this knowledge gap, providing valuable information on the relationship between ustekinumab exposure during the induction phase and clinical outcomes in this patient population. Additionally, our study identifies factors associated with low ustekinumab concentration exposure, offering useful information on risk groups for potential pharmacokinetic and likely clinical failure. Despite our data supporting the correlation between higher UTL and improved clinical outcomes, there is limited evidence to support proactive optimization of therapy to achieve a higher serum concentration resulting in improved clinical outcomes[30, 31]. Further studies are needed to clarify the role of proactive TDM and dose adjustment of UST therapy in achieving clinical outcome

In conclusion, our study has demonstrated a significant association between UST concentrations and clinical and biochemical remission in patients with IBD. Our findings support the idea that the induction doses established in the drug label may not be sufficient for all patients, and we have identified subgroups of at-risk patients, such as those with higher body weight, increased inflammatory burden, and greater severity of baseline disease. These results underscore the importance of considering treatment individualization and monitoring UST concentrations in IBD patients to optimize clinical outcomes.

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	N(%) patients
Age (mean, SD)	48.60 (17.0)
Gender, n (%)	
Female	24 (42.9)
Male	32 (57.1)
Weight (Kg) (mean, SD)	74.2 (14.3)
FFM (mean, SD)	73.8 (14.0)
BMI (mean, SD)	25.8 (4.4)
Previous IBD-related surgery , n (%)	10 (22.2)
Previous biological therapy,	51 (91.1)
IBD type, n (%)	
CD	45 (80.4)
UC	11 (19.6)
CD location, n (%)	
L1 (ilieal)	24 (42.9)
L2 (colonic)	1(1.8)
L3 (ileocolonic)	19 (33.9)
CD behaviour, n (%)	
B1 (inflammatory)	15 (33.5)
B2 (stricturing)	17 (37.8)
B3 (penetrating)	13 (28.9)
UC location, n (%)	
E2 (left-sided colitis)	5 (8.9)
E3 (pancolitis)	6 (10.7)
Perianal disease, n (%)	10 (22.2)
CPR baseline (median, IQR)	0.4 [0.4]
FCP baseline (median, IQR) (n=82)	503.7[1035.9]
Albumin baseline (median, IQR),(n=87)	4.3 [0.6]
Hemoglobin baseline (median, IQR), n=85	13.4 [2.2]
Extraintestinal manifestations, n (%)	10 (17.9)
Disease activity	
Mild	10 (17.9)
Moderate	30 (53.6)
Severe	15 (26.8)
Remission	1 (1.8)

Table 1. Demographic and clinical characteristics of the study population (n=56)

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BMI: body mass index, FFM: fat-free mass; CD: Crohn's disease; UC: ulcerative colitis; SD: standard deviation; IQR: interquartile ranges; CRP: C-reactive protein; FCP: faecal calprotectin

Table 2. Ustekinumab trough levels and clearance estimates in the induction period by patient characteristics

	UTL (µg/mL)	**p**	**Clearance (L·day-1)**	**p value**
Gender, n (%)				
Female	10.0 [5.7]	0.010	0.44 [0.21]	0.001
Male	5.2 [6.5]		0.62 [0.16]	
IBD type				
CD	7.6 [8.3]	0.926	0.53 [0.24]	0.404
UC	8.1 [4.4]		0.62 [0.13]	

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Naïve to biological treatment				
Yes	12.0 [13.2]	0.139	0.41 [0.42]	0.039
No	7.6 [7.3]		0.56 [0.22]	
Perianal disease				
No	7.6 [8.1]	0.717	0.53 [0.23]	0.883
Yes	7.1 [9.7]		0.52 [0.26]	
Previous IBD-related surgery				
No	7.2 [7.7]	0.436	0.57 [0.21]	0.675
Yes	9.4 [6.2]		0.51 [0.24]	
Acitvity disease				
Mild	11.6 [9.8]		0.46 [0.24]	
Moderate	6.7 [6.5]	0.013*	0.58 [0.22]	0.172
Severe	4.3 [7.0]		0.56 [0.24]	
Biochemical parameters				
FCP baseline (n=46)	-0.293	0.048	0.24	0.108
Albumin baseline (n=51)	0.050	0.729	0.02	0.875
Hemoglobin baseline (n=51)	-0.218	0.124	-0.14	0.923
Weight (n=56)	-0421	0.001	0.722	<0.001
BMI (n=56)	-0.360	0.009	0.566	<0.001
FFM (n=56)	-0.457	<0.001	0.777	<0.001

UTL: ustekinumab trough levels; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; FCP: faecal calprotectin; BMI: body mass index, FFM: fat-free mass

*significant difference in ustekinumab trough levels between severe and mild disease

Table 3. Estimated pharmacokinetic parameters of UST during the induction period

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	All	CD (n=45)	UC (n=11)	p value
UTL (µg/mL)	7.8 [7.3]	7.6 [8.3]	8.1 [4.4]	0.926
IPRED, µg/mL	7.9 [5.1]	7.7 [8.2]	8.2 [4.3]	0.926
Kel, day^{-1}	0.11 [0.03]	0.11 [0.04]	0.12 [0.02]	0.688
Vc, L	4.83 [0.71]	4.75 [0.7]	5.1 [0.8]	0.097
Vp, L	4.01 [0.74]	3.96 [0.75]	4.17 [0.52]	0.359
Cl, $L \cdot day^{-1}$	0.55 [0.22]	0.53 [0.24]	0.62 [0.13]	0.404
T1/2, day	6.19 [1.89]	6.30 [2.14]	5.85 [1.09]	0.688
AUC, µg·day/mL	761.6 [274.9]	770.1 [308.6]	759.9 [184.4]	0.529

AUC: area under the concentration-time curve CD: Crohn's disease; UC: ulcerative colitis; UTL: ustekinumab trough levels; IPRED; IPRED: individual model predicted concentrations; Kel: elimination-rate constant; Vc: central distribution volume; Vp: peripheral distribution volume; Cl: clearance; T1/2: elimination half-life.

Table 4. Univariate and multivariate analysis of the factors associated with achieving optimal ustekinumab exposure (UTL > 8 µg/mL) at week 8.

	Bivariate analysis OR [95% CI]	p value	Multivariate analysis OR (95% CI)]	P value
Female	5.3 [1.68-16.96]	0.004	4.56 [1.12-18.60]	0.034
CD	1.15 [0.31-4.31]	0.838		
Previous IBD-related surgery	2.63 [0.69-10.05]	0.157		

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Perianal disease	1.06 [0.26-4.32]	0.936		
No previous exposure to biological therapy	1.69 [0.26-10.97]	0.584		
Albumin baseline <3.5 g/dL	1.04 [0.14-8.04]	0.967		
FCP baseline< 500 µg/g	7.2 [2.11-24.56]	0.002	7.72 [1.75-34.03]	0.007
Weight	0.94 [0.90-0.98]	0.007	0.98 [0.87-1.11]	0.787
FFM	0.93 [0.88-0.98]	0.003	0.94 [0.89-1.00]	0.055

CD: Crohn's disease; FCP: faecal calprotectin; FFM: fat-free mass

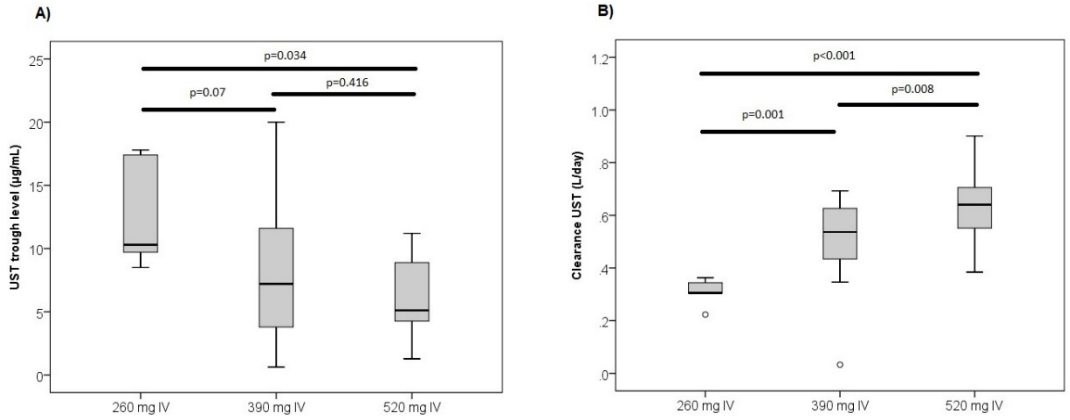

Figure 1. Relationship between UST trough levels and (A) induction doses (based on body weight) and (B) clearance in inflammatory bowel disease. UST: ustekinumab.

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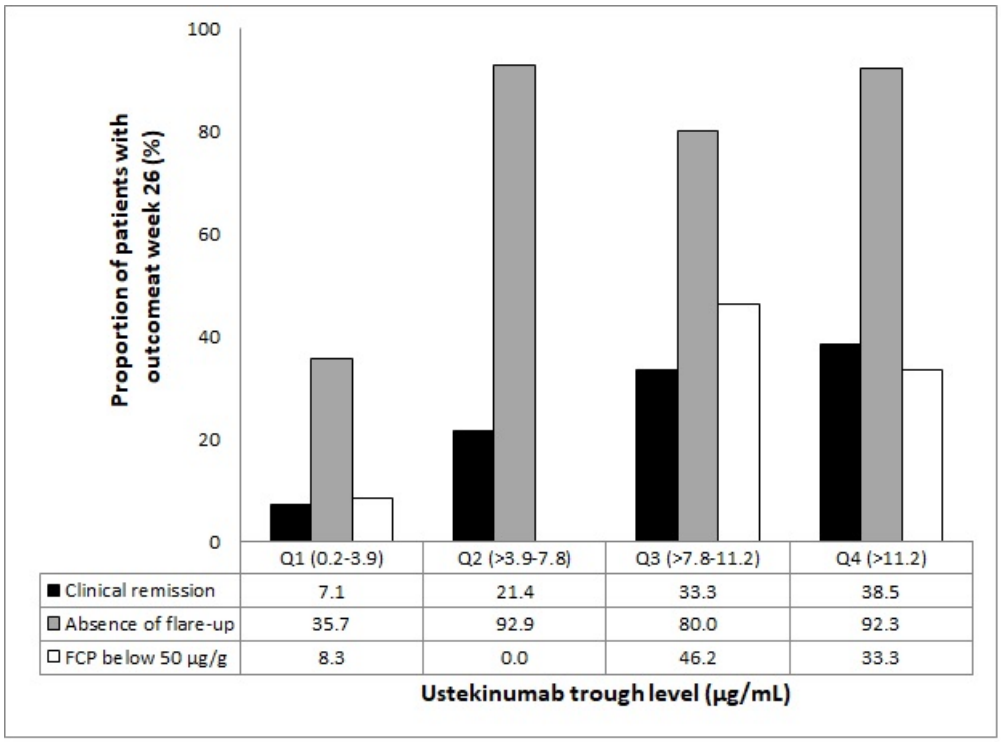

Figure 2. Proportions of patients achieving efficacy outcomes at week 26 stratified by UST trough levels quartiles during the induction phase. UST: ustekinumab