

# Evaluation of ustekinumab trough levels during induction and maintenance therapy with regard to disease activity status in difficult to treat Crohn Disease patients

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## Research article

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# Abstract

**Background** Ustekinumab (UST) is approved for the therapy of moderate and severe Crohn disease (CD). Therapeutic drug monitoring (TDM) helps to monitor the therapeutic effect of biologics. Therefore, the aim of this study was to evaluate clinical outcomes of UST treated CD patients and to determine UST trough level (USTTL) with clinical and corticosteroid-free remission.

**Methods** This retrospective study of CD included patients with moderate and severe active disease treated with a weight adapted induction dose of UST intravenously. The maintenance therapy consisted of 90 mg UST subcutaneously at week 8 and thereafter every 8 or 12 weeks depending on the clinical response. Clinical and corticosteroid-free remission, Harvey-Bradshaw-Index (HBI), USTTL and further laboratory parameters were measured just before the injection of UST at each follow-up evaluation until week 40.

**Results** 37CD patients with a median HBI of 9 at week 0 were included. Starting from 24% at the beginning of the monitoring period and 38% of patients at the end of it, were treated with an 8-week interval ( $p = 0.18$ ). There was a significant improvement of clinical ( $p = 0.0004$ ) and corticosteroid-free remission ( $p = 0.03$ ) as well as in HBI ( $p < 0.0001$ ) from week 0 until the end of the observation period, respectively. The serum USTTL decreased significantly from 2.0 at week 8 to 0.3 in the maintenance therapy and 0.4  $\mu\text{g/mL}$  at the end of it ( $p < 0.0001$ ), respectively. Neither USTTL nor levels of CRP or faecal calprotectin were associated with disease outcome. Concomitant immunomodulator therapy did not appear to affect the USTTL or the clinical course.

**Conclusions** UST is an effective treatment option in difficult to treat CD patients. USTTL may not be associated with treatment efficacy or predict treatment outcomes in CD patients. Further prospective randomized trials should be conducted to evaluate if USTTL is associated with treatment outcomes in CD patients.

## Background

Crohn's Disease (CD) is an inflammatory bowel disease characterized by a transmural segmental inflammation of the gastrointestinal tract. The clinical course of CD involves chronic inflammation resulting in abdominal pain, chronic diarrhea, gastrointestinal bleeding, and complications including the development of strictures and fistulas. To date, the pathogenesis remains not fully understood and there is currently no cure for CD. The treatment consists of administering immunomodulating therapy, like corticosteroids, immunosuppressants and biologic agents, such as tumor necrosis factor alpha (TNF- $\alpha$ ) antagonist, integrin and interleukin inhibitors [1]. Unfortunately, surgery has no curative effect on CD, and most patients require treatment with different therapies during their lifetime. The use of biologic agents has revolutionized the therapy of CD [2]. Ustekinumab (UST) is a biologic agent approved for the treatment of moderate and severe CD, even for patients with a previous history of anti-TNF- $\alpha$  treatment.

UST inhibits the p40 subunit of interleukin(IL)12 and IL23 [3]. In the clinical care the majority of the patients with CD have been already exposed to anti-TNF- $\alpha$  or other immunomodulatory therapies.

Therapeutic drug monitoring (TDM) is an important key player in the current inflammatory bowel disease (IBD) therapy and it is recommended when using anti-TNF- $\alpha$  agents, like adalimumab and infliximab [4]. There are two ways to conduct TDM, the first one is proactive, in which the TDM is made even in the absence of IBD-related symptoms. The other one is reactive, where TDM is determined only when the patient has a flare of IBD [4]. Existing data regarding the UST and TDM has been the result of highly selected patient groups from approval studies or from studies where the observational time was short [5].

Because of the scarce data regarding TDM and partially conflicting results between the data from the approval and real-life studies, we decided to investigate the association of serum UST level with clinical and corticosteroid-free remission in CD patients after induction and maintenance therapy.

## Methods

### Study Population

We retrospectively assessed a prospectively maintained database of CD patients treated at our center. Our cohort consisted of 37 consecutive patients with CD receiving UST in a German University Medical Center. Furthermore, patients were included only if they had an available USTTL at week 8 after induction therapy as well as a second measurement during maintenance therapy. Harvey–Bradshaw Index (HBI) was used for the clinical assessment of CD. Clinical remission was defined by a HBI<5 points. Corticosteroid-free remission was defined as achieving clinical remission with a complete withdrawal of steroids in patients who had previously a cortisone therapy at the time of UST induction.

Following biochemical parameters were analyzed: hemoglobin level, platelet and leukocyte count, CRP level (normal< 5 mg/l), fecal calprotectin (FC) level (normal <50mg/Kg) and UST trough levels in serum. The blood laboratory values were determined immediately before the administration of UST.

UST was administered according to the approved protocol. Induction was made with intravenously, weight adapted doses (less than 55 kg 260mg, between 55Kg and 85Kg 390 mg, more than 85Kg 520 mg). The maintenance therapy was performed by administering 90mg UST subcutaneously at week 8 after the induction therapy and thereafter every 8 or 12 weeks depending on the clinical response. The UST interval was shortened only in cases of clinical disease activity. The following treatment intervals were defined: T0 (time of induction), T1 (8 weeks after induction), T2 (16-20 weeks after induction), T3 (24-28 weeks after induction) and T4 (32-40 weeks after induction). The induction and maintenance UST therapy was administered exclusively by medical staff at the university medical center. Week 32 to 40 was chosen to assess the outcome of UST induction and maintenance because it also included patients with delayed clinical response to UST. Response to therapy was defined: 1) an HBI-reduction of 3 points or more; 2) normalization of or reduction of CRP levels of at least 50% compared to baseline concentration or 3) normalization of FC (< 250 mg/kg), in patients with elevated baseline concentrations >500 mg/kg.

Serum concentrations of CRP, hemoglobin, platelets and leukocyte count were determined by utilizing the automated systems of the Central Laboratory of the Department of Clinical Chemistry at University Medical Center Goettingen. FC levels were measured as previously described [6].

The quantification of UST in serum samples was performed using an enzyme immunoassay (IDKmonitor® UST drug level Enzyme-linked immunosorbent assay[ELISA], Immundiagnostik AG, Germany) according to the manufacturer's recommendations. The lowest quantifiable concentration in a sample for this method was 0.3 µg/mL. Serum UST levels were determined by an external laboratory. The determination method was established and validated as a routine procedure.

## **Ethic Statement**

This study was approved by the local ethics committee (approval number 7/10/19).

## **Statistical analysis**

Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as percentages. For comparisons of variables a nonparametric 1-way analysis of variance based on the median score was used for continuous and ordinal variables, whereas a Fisher exact test was used for categorical variables. A *P value* <0.05 was considered as statistically significant. We further performed a Spearman's correlation between continuous variables. Statistical analysis and figures were done using the SPSS 26 software for Mac OS (SPSS, Chicago, Illinois, USA) and GraphPad Prism 5.

## **Results**

From a total of 37 CD patients at the time of induction, 25 were male with a median disease duration of 15 years. The majority of patients were between 17 and 40 years old at the first diagnosis of CD. They had mostly an ileocolonic and a penetrating or perineal involvement. 51% of the patients had corticosteroids, 14% Azathioprine and 30% Tacrolimus as concomitant therapy. 57% received UST as a monotherapy. 6, 24 and 7 patients received an UST induction dose of 260 mg, 390 mg or 520 mg, respectively. All patients were previously exposed to a TNF-α antagonist (Table 1). Following parameters were recorded at the time of induction therapy: the median HBI was 9 and the median serum albumin level was 3.5 g/dL, the median platelet and leukocyte count were  $313 \times 10^3/\mu\text{L}$  and  $8.5 \times 10^3/\mu\text{L}$ , respectively, as well as the median serum CRP level was 6.9 mg/L and median FC level 458 mg/Kg (Table 2).

	Total (n=37)
Median Age, year (IQR)	48 (33-55)
Female / Male, n (%)	25 / 12 (68/32)
Median disease duration, yr (IQR)	15 (7-22)
Montreal age at diagnosis of CD: A1 / A2 / A3, n (%)	10 / 23 / 4 (27/62/11)
Montreal disease behavior of CD: B1 / B2 / B3 / B3p, n (%)	10 / 6 / 6 / 15 (27/16/16/41)
Montreal localization of CD: L1 / L2 / L3 / L4, n (%)	7 / 4 / 21 / 5 (19/11/57/13)
Medication profile, n (%)	
Steroids	19 (51)
Azathioprine	5 (14)
Tacrolimus	11 (30)
Therapy, n (%)	
Monotherapy	21 (57)
Combinationtherapy	16 (43)
Endoscopic activity <sub>1</sub> , n (%)	25 (68)
Initial Ustekinumab dose, n (%)	
260 mg	6 (16)
390 mg	24 (65)
520 mg	7 (19)
History of TNF- $\alpha$ antagonist use, n (%)	37 (100)

IQR: interquartile range; CD: Crohn disease; HBI: Harvey-Bradshaw Index;  
CRP: C-reactive protein; <sub>1</sub>25 patients with available endoscopic evaluation

At the time of induction therapy, 11% of the patients were in clinical remission. All of these patients had a therapy consisting of an immunomodulator or corticosteroid. Moreover, three of these patients showed a corticosteroid dependent course. The rate of clinical remission increased significantly during the maintenance therapy from 41% at T1 to 54% at T4 ( $p=0.0004$ ) (Figure 1A). The rate of corticosteroid-free remission at the time of induction was 6% and increased significantly during the maintenance therapy to 33% at T4 ( $p=0.03$ ) (Figure 1B).

During maintenance therapy the median HBI decreased significantly from 9 at the time of induction to a median HBI of 5 between T1 to T3 and at the end of the study to a median HBI of 4 at T4 ( $p<0.0001$ ) (Table 2).

Repeated evaluation of serum albumin level ( $p<0.19$ ), platelet ( $p<0.93$ ) and leukocyte ( $p<0.68$ ) count as well as CRP ( $p<0.91$ ) or FC ( $p<0.32$ ) levels did not change over time (Table 2). Repeated measurement of median serum USTTL decreased significantly after the intravenously induction dose from 2.0 to 0.3, 0.3 and 0.4 at T2, T3 and T4 ( $p<0.0001$ ), respectively. There was no significant change in the rate of combination therapy ( $p<0.75$ ) or application interval of UST therapy ( $p<0.18$ ) (Table 2).

Table 2. Baseline and dynamics of the clinical and laboratory parameters during the therapy with Ustekinumab

	T0	T1	T2	T3	T4	P Value
Median HBI, (IQR)	9 (8-12)	5 (2-7)	5 (2-10)	5 (2-8)	4 (3-8)	<0.0001
Median Albumin level, g/dL (IQR)	3.5 (3.1-3.7)	3.7 (3.4-3.9)	3.7 (3.4-3.9)	3.7 (3.4-3.9)	3.7 (3.4-3.9)	0.19
Median platelet count, $10^9/\mu\text{L}$ (IQR)	313 (227-436)	306 (233-385)	318 (248-380)	306 (261-388)	300 (239-361)	0.93
Median leukocyte count, $10^9/\mu\text{L}$ (IQR)	8.5 (6.7-10.8)	9.5 (7.3-12.1)	8.6 (7.3-12.1)	10.4 (7.8-12.2)	8.6 (6.6-11.8)	0.68
Median CRP level, mg/L (IQR)	6.9 (2.8-14.6)	5.4 (1.8-15.1)	5.7 (2.3-19.6)	6.2 (2.5-17.9)	6.8 (3.0-17.6)	0.91
Median FC level, mg/Kg (IQR)	458 (347-702)	225 (74-448)	391 (126-1032)	283 (66-444)	267 (96-479)	0.32
Median UST level, $\mu\text{g/mL}$ (IQR)	NA	2.0 (1.2-4.0)	0.3 (0.3-0.4)	0.3 (0.3-0.6)	0.4 (0.3-0.8)	<0.0001
Combinationtherapy, n (%)	16 (43)	17 (46)	14 (38)	16 (43)	15 (41)	0.75
UST 8 week interval	NA	9 (24)	11 (30)	13 (35)	14 (38)	0.18

HBI: Harvey-Bradshaw-Index; IQR: interquartile range; CRP: C-reactive protein; UST: Ustekinumab; <sub>1</sub>number of patients in remission in relation with number of patients taking cortisone therapy

The median serum USTTL at T1 were 1.9 and 2.0 µg/mL in patients with clinical remission and active disease (p=0.57). In patients who achieved a clinical remission and those with active disease the median serum UST trough levels decreased during maintenance therapy to 0.3 and 0.3 µg/mL at T2 (p=0.90), 0.3 and 0.3 µg/mL at T3 (p=0.76) as well as to 0.4 and 0.5 µg/mL at T4 (p=0.75), respectively. The USTTL measured at T1 neither enabled a prediction of clinical remission to induction therapy for T2 (p=0.54), T3 (p=0.15) or T4 (p=0.58) nor was it associated with corticosteroid-free remission at T1 (p=0.05), T2 (p=0.23), T3 (p=0.31) or T4 (p=0.40), respectively. A nonparametric 1-way analysis of variance showed no association with disease activity status for median serum USTTL (p=0.88, Figure 2A), CRP levels (p=0.69, Figure 2B) and FC levels (p=0.53, Figure 2C).

Finally, we performed Spearman's correlation between serum USTTL and serum albumin, platelet and leukocyte count as well as CRP and FC levels. There were no correlations between these parameters (data not shown).

## Discussion

The proinflammatory cytokines IL12 and IL23 have been implicated in the pathophysiology of CD with multiple lines of evidence suggesting that CD is mediated by Th1 and/or Th17 cells [6, 7]. UST prevents IL12 and IL23 bioactivity by preventing their interaction with their cell surface receptor protein IL12Rb1. Through this mechanism of action, UST effectively neutralizes IL12 (Th1)- and IL23 (Th17)-mediated cellular responses. UST binds with high affinity to the p40 subunit of human IL12 and IL23 and has recently been approved for the treatment of moderately to severely active CD in adults.

Currently, UST is an effective treatment for anti-TNF-α refractory CD patients. As it has been shown to be useful in the management of patients with a loss of response to anti-TNF-α agents. However, there are limited data on the association of UST drug concentrations on CD patient outcomes. Understanding UST pharmacokinetic characteristics and the relationship between clinical outcomes and UST concentration is important for prescribers to optimize efficacy of UST therapy.

The main finding of this study is that anti-TNF-α refractory CD patients treated with UST achieved in 54% and 33% of cases clinical and corticosteroid-free remission over a treatment period of 32 to 40 weeks. In addition, the UST trough level decreased significantly during the maintenance therapy just above the detection limit. The mean UST concentration at week 8 in our study was similar to the value reported by Adedokun et al.: 2.0 (IQR 1.2-4.0 µg/mL) [5]. Interestingly, the present real-life study does not report a positive relationship between USTTL and clinical disease outcomes during UST therapy. In addition, the levels of proinflammatory biochemical parameters such as CRP and FC neither decreased during the treatment period nor were associated with treatment outcome. The majority of the included patients were treated with a 12-week interval during the maintenance therapy.

Our findings show discrepancy from those found in previous studies in which an UST trough level of higher than 4.5 µg/mL at week 26 was associated with endoscopic response [9] or a trough level of 3.3 µg/mL at week 8 was associated with clinical remission [5]. In line with our results, the study by

Battat et al. also failed to identify an association of UST trough level with clinical outcomes [9]. Another study by Thomann et al. also identified that serum UST level at week 8 was moderately effective to predict clinical response for week 16 [10].

The pharmacokinetics post hoc analysis of the approval studies of UST published by Adedokun et al. showed that during the maintenance study period UST concentration reached a steady state after the second maintenance dose. Moreover, the median trough concentration in patients given UST every 8-weeks compared to patients every 12-weeks was approximately threefold higher [5]. UST serum concentrations were significantly associated with rates of clinical remission only in patients treated with an 8-week interval ( $p = 0.006$ ) but not with a 12-week interval application ( $p = 0.08$ ). In contrast to the results of the present study, they could show that trough concentrations of UST of  $0.8 \mu\text{g/mL}$  or greater were associated with maintenance of clinical remission. In addition, the UST concentration cutoffs obtained from the receiver operator curve analyses were based on statistically significant but modest area under the curve and specificity values [5]. Because the level of significance could only be achieved only in the 8-week interval treatment, this result has no general validity in a real-life setting, as the majority of patients may be treated with a 12-week interval.

In accordance with our results, Peinchart et al. showed, by studying on 49 Patients within maintenance therapy, that USTTL did not correlate with clinical, biological or endoscopic response [11].

There are various factors that may account for such differences including distinct treatment regimens and disease outcome assessments, different assays of measuring UST, and distinct patient populations. Only studies by Adedokun et al., Thomann et al., Soufflet et al. and ours evaluated CD patients after intravenous induction and subcutaneous maintenance therapy [5, 10, 12] while other published studies evaluated different modes of induction and maintenance therapy [11, 9].

There are different assay techniques available on the market to determine the UST drug concentration and the above mentioned studies did not use the same assay to determine the UST cutoffs, which may explain the different results that were obtained. The assays in the previous works are using laboratory techniques like ELISA, a drug-tolerant liquid-phase homogeneous mobility shift assay, or an electrochemiluminescent immunoassay [5, 9, 11]. In our study we used an ELISA assay. Thus, other prospective studies are needed to confirm therapeutic UST trough levels.

In our cohort, all patients were previously treated or were intolerant to anti-TNF- $\alpha$ . The anti-TNF- $\alpha$  therapy was changed due to anaphylaxis, primary and secondary nonresponse or side effects. In the UST-approval studies the medical history of anti-TNF- $\alpha$  therapy of the patients was associated with lower rates of clinical remission [3]. The fact that we have only included anti-TNF- $\alpha$  exposed patients in our study with high inflammatory burden and complex pathophysiology could explain the contrasting results of our study.

In contrast to the experience with anti-TNF- $\alpha$  there was no significant impact of immunomodulators such as azathioprine or tacrolimus on serum UST concentration in the present study as well as previously

published [5, 9].

We acknowledge the limitations of our study, such as the retrospective characteristic, the small number of patients in our cohort and the fact that not all patients received endoscopic observation or FC monitoring in the analyzed period. Due to the small number of patients, we could not calculate the UST trough level for the group of patients treated with an 8-week interval compared to the 12-week interval. However, we strongly believe that our results bring important clinical information, which could potentially help gastroenterologists treating CD with UST make important decisions.

## Conclusions

UST is a valid and helpful agent in the therapy of difficult to treat patients with CD. In our cohort, the serum USTTL did not correlate with clinical or corticosteroid-free remission, with UST trough level ranging just above the detection limit during maintenance therapy. Further large-scale real-life studies are needed to clarify the value of UST TDM for the therapy of CD.

## List Of Abbreviations

UST	Ustekinumab
CD	Crohn disease
TDM	Therapeutic drug monitoring
USTTL	Ustekinumab trough level
HBI	Harvey-Bradshaw-Index
CRP	C reactive protein
IL	Interleukin
TNF- $\alpha$	Tumor necrosis factor alpha
IBD	Inflammatory bowel disease
FC	Fecal calprotectin
IQR	Interquartile range

## Declarations

### Ethical approval and consent to participate

This study was approved by the Ethics Committee at the University Medical Center Goettingen (approval number 7/10/19).

### Consent for Publication

Not applicable

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Competing interest

The authors declare that they have no competing interests.

## Funding

The authors declare that they have no competing interests.

## Authors' contribution

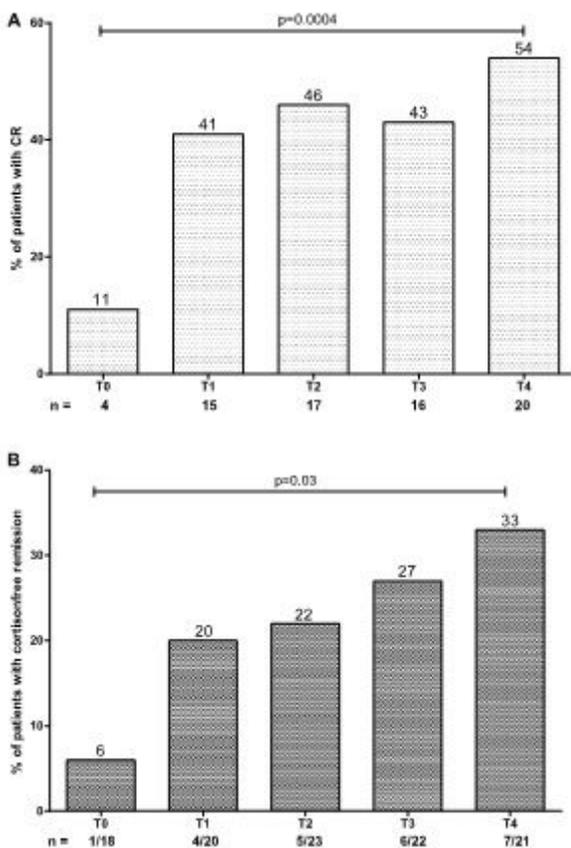
AA conceived the study, analysed and interpreted the data and edited the manuscript. NCM assisted in data analysis, and wrote the manuscript. MB acquired the data and contributed to the statistical analysis. NCM, MB, EM, SK, VE and YP edited significant sections and revised the manuscript. All authors read and approved the final version of the manuscript.

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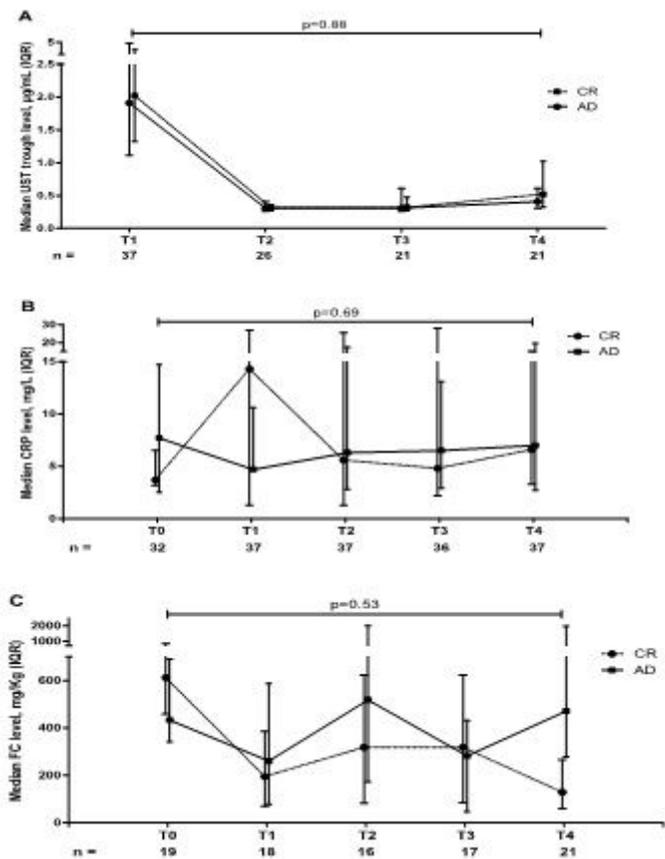
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## Figures



**Figure 1**

Clinical (A) and corticosteroid-free (B) outcomes in CD patients receiving UST. T0-baseline, UST-induction time, T1- 8w after i.v. induction, first s.c. application, T2, T3,T4 further s.c. applications as maintenance therapy



**Figure 2**

Association of clinical disease status (CR- clinical remission, AD-active disease) and UST- Ustekinumab trough levels (A), CRP- C reactive protein (B), FC- fecal calprotectin (C), IQR-interquatile range