Early measurements of serum ustekinumab concentrations predict efficacy for remission in patients with Crohn’s disease

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Abstract

Ustekinumab concentrations at week 4 and beyond have been associated with treatment outcomes in patients with Crohn’s disease. However, the exposure-response relationship during the first 2 weeks of treatment is unclear. We summarize the @GIJournal discussion held on November 10, 2021, during which we discussed the article by Hanžel et al. entitled “Peak concentrations of ustekinumab after intravenous induction therapy identify patients with Crohn's disease likely to achieve endoscopic and biochemical remission”[1]. Key findings were critically reviewed by our experts E. V. Loftus, Jr., and A. Charabaty, and the session was moderated by S. Mahmood.

Introduction

Ustekinumab (UST) concentrations at week 4 and later correlate with treatment outcomes in clinical trials and real-world applications. However, little is known about the relationship between UST exposure parameters during the first 2 weeks of treatment and clinical outcomes of patients with Crohn’s disease (CD). A shorter dosing interval to every 4 weeks has been proposed to optimize UST treatment (e.g., STARDUST [NCT03107793][2]); therefore, it would be clinically
informative to identify patients who would benefit from this dosing regimen at an earlier time point (i.e., during the first 2 weeks), such as those unlikely to experience endoscopic remission with the current dosing regimen.

**Article Summary**

Hanžel et. al.\(^1\) performed a prospective observational study investigating the relationship between serum concentrations of UST during the first 2 weeks of treatment and endoscopic and biochemical remission in patients with CD.

The study comprised 41 consecutive patients at a single center from October 2017 through January 2019 who received treatment with UST (~6 mg/kg body weight, intravenously [IV], then 90 mg subcutaneously [SC] every 8 weeks) because of endoscopic markers of active CD. During the first 2 weeks, the peak concentration of UST was measured immediately after IV infusion and at week 2; the area under the concentration-time curve through week 2 was determined. The associations between these parameters and endoscopic remission (Simple Endoscopic Score for CD scores of 3 or less without ulceration, assessed centrally) and biochemical remission (level of fecal calprotectin of <100 mg/kg) were evaluated using the Mann-Whitney U test.

Hanžel et. al.\(^1\) reported that endoscopic remission was achieved in 10/41 patients (24.4%) at week 24. Peak UST concentrations were associated with endoscopic remission (area under the receiver operating characteristic curve, 0.717; 95% confidence interval [CI], 0.517–0.916). Notably, endoscopic remission was achieved in 6 of 13 patients (46%) with a peak concentration of >105 μg/mL (upper tercile) but in only 1 of 14 patients (7%) with a peak concentration of <88 μg/mL (lower tercile). Biochemical remission at week 24 was achieved in 21/41 patients (51.2%) and was apparent in 17/41 patients (41.5%) at weeks 16 and 8. All exposure parameters during the first 2
Discussion Summary

weeks were associated with biochemical remission. Biochemical and endoscopic remission were similarly associated with peak and week-2 UST concentrations, the area under the curve through week 2, and measures at weeks 4 and 8. These data indicate that UST concentrations measured during the first 2 weeks of treatment and concentrations measured at week 4 or later similarly predict clinical outcomes. Thus, early administration of UST may help guide treatment. The authors suggested the UST therapy could be optimized by earlier administration of the first SC dose or as maintenance dosing every 4 weeks. The relatively small sample size and the single center design were study limitations. Additionally, the findings cannot be extrapolated to biologic-naïve patients.

Discussion

The session was moderated by Dr. Sultan Mahmood (SM). Key findings were critically reviewed by E. V. Loftus, Jr., (EVL [@EdwardLoftus2]) and A. Charabaty (AC [@DCharabaty]).

Per the pre-discussion poll conducted by SM, 26.4% of the 72 participants were inflammatory bowel disease specialists, 36.1% were general gastroenterology or colorectal surgeons, 33.3% were fellows or trainees, and 4.2% were advance practice providers, Doctor of Pharmacy, or nurses.

SM: Pre-discussion poll Q1: In the UNITI Maintenance RCT³, CD patients who had a response to IV UST induction were randomized to SC maintenance vs. placebo [arms]. Compared to a placebo rate of 36%, patients on UST SC every 8 weeks had [which of] the following remission rate at week 44?
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Of the 60 respondents, 46.7%, 30%, 16.7% and 6.7% answered 53%, 43%, 63%, and 33%, respectively.

**SM: Pre-discussion poll Q2: According to a posthoc analysis of phase 2 and 3 UST trials in CD⁴, what UST trough level has been associated with a higher proportion of patients maintaining clinical remission?**

Of the 76 respondents, 44.7%, 35.5%, 13.2%, and 6.6% answered >2.5 μg/mL, >7.5 μg/mL, >1 μg/mL, and >10 μg/mL respectively.

[@PerelmansPearls:](https://twitter.com/PerelmansPearls) Nice! [It’s] interesting they mentioned baseline albumin correlation with a lower level, but I didn’t think there was a significant difference. Also, [I was] generally disappointed with the biochemistry performance showing remission vs. endoscopy. Lastly, I would love to see histological remission as an endpoint since new “norm.”

[@ShimaghavimiMD:](https://twitter.com/ShimaghavimiMD) Modifications in the composition of mucosal immune cells in response to therapeutic pressure are able to promote a molecular resistance.⁵ Therefore, histologic, endoscopic, and clinical remission are all paramount for evidence-based medicine patient care for IBD patients.

**SM: Q1. What is your current practice of proactively checking drug levels with UST induction? Do you check drug level before the first or the second SC dose?**

On the poll, 75.4% of 65 respondents reported they don’t check drug levels, 13.8% noted they check at 7-8 weeks post IV dose, 3.1% at 4 weeks post IV dose, and 7.7% at 4 weeks post SC dose.
@PerelmansPearls: Not too many people are on UST for me; the ones that are [on UST] are doing well, so [I] haven’t needed [to check it].

@ChrisAndersonM4: I usually don’t check levels. [I’m] wondering what the experts do?

@AsadurRahman87: Thanks for sharing this new interesting data. What we do not know is whether more frequent dosing of UST in patients with a low drug level leads to capture of the response. So, I am on the fence for proactive monitoring, but with more comparative long-term data, the practice may change.

EVL: Extremely interesting and provocative article. For UST, I have tended to be way more “reactive” in my therapeutic drug monitoring (TDM) [than for] infliximab or adalimumab.

@ijlalakbar: Is that because of lack of proactive monitoring data in UST or the abundance of data in anti-TNF? Or both?

EVL: Both!

EVL: These data, albeit small numbers, make me wonder about the utility of checking a week-2 level. What do people think?
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@ptandonGI: Or even peak levels 1 hour after the IV dose, [it] saves the patient an additional visit back and seems to have a similar benefit? The question is whether accelerating to every 4 weeks in those with lower levels at this time point is enough to capture the response!

EVL: Good point—this paper suggests that lower levels result in less response, but we don’t know if dose escalating them will help.

@PerelmanaPearls: Are these being covered in the community (have seen mixed results)? Also, dose escalation has been such a battle!!!

@GI_PharmaD: Clinically (if validated), with proper therapy adjustments, this practice could have the potential to help capture remission sooner, which is definitely a patient-centered outcome.

DC: I consider “induction” IV dose + 1st SC dose. I have not been checking UST level at induction to predict response. I do check CRP/FCP 4–6 weeks after the IV dose to check objective response. What do others do?

EVL: Agree, hasn’t been my clinical practice to check levels this early.

@BattatMD4IBD: Peak week 2 levels are interesting; [it is] difficult to get a 2nd IV dose 2 weeks from the 1st. I use UST levels in maintenance. UNITI TDM data (-1 mg/mL) doesn’t apply to the real world. Janssen assay doesn’t translate to the assays we use. Two studies using HMSA exist⁴,⁶; both show 3.8–4.5 [μg/mL] associated with outcomes.
@ijlalakbar: If inflammatory markers are not going down, do you escalate or check levels then?

**EVL:** Both approaches are reasonable. I used to check levels, but given low immunogenicity, I had been recently inclined to make that decision clinically.

**DC:** I check level if there’s no response after adjusting therapy, @ijlalakbar. If partial response or loss of response, I escalate to every 4 weeks or do another IV response.

@waqqasafif did work on that. Did the UST level before adjustment help predict who will respond to extra IV and SC every 4 weeks?

**@GI_PhamD:** From a prior auth[orization] perspective, I have seen appeals denied for every 4-week dose escalation due to the request for UST level. So not normally performed in practice, but [I] sometimes will get it for the sake of trying to get every 4-week dose approved.

@waqqasafif: Unfortunately no! Almost all the patients had trough concentrations >1 mg/mL, and despite “adequate” concentrations, patients responded to the IV reinduction.

**DC:** TY @waqqasafif! Which makes checking UST level during maintenance less helpful to guide management and predict the response to a re-induction dose. This article suggests that maybe checking the level during induction could be helpful.
@AsadurRahman87: Thanks for sharing this valuable experience, @waqqasafif. How long after the IV reinduction do you introduce SC dosing?

@mtahirMD: Do we know if these assays are drug tolerant? @EdwardLoftus2: At what levels do you give up and change the drug class, let’s say in severe CD phenotype?

**EVL:** For sure, a level of less than 1 μg/dL [0.01 μg/mL] at week 8 is low and, for sure, levels of greater than 4 are high. Lots of grey area.

@IBDPharmacist: In patients with potentially higher drug clearance (high CRP, BMI, low ALB) you would consider pro-active UST therapeutic drug monitoring?

**EVL:** Maybe after reading this paper—but it would be nice to have confirmatory papers

@IBDImmunology: One thing I do consider: propensity for anti-drug formation. Infliximab >> adalimumab >>>> UST or vedolizumab (VDZ).

Small molecules = none!

@guthealthmd: Add to discussion.

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**SM:** Q2. Are you more inclined to check levels if there is no/partial response to the induction IV dose or first subcutaneous dose? If so, when?
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@ShimaghavimiMD: Usually I check the level if there is no/partial response for UST or Entyvio; [I’m] wondering what the other experts do

DC: Based on this article, I might be more inclined to check in CD with prior loss of response/no response to other biologic—difficult to treat CD (which is the population of this study)—only if we think that changing the frequency of SC injection to every 4 weeks will help achieve remission

EVL: I think one of the issues with UST is the “chasm” between week 0 and week 8—“don’t just stand there, do something”—less of an issue with CD than UC—I am not answering your question though—“it depends.”

@AsadurRahman87: I don’t think there is strong data, but it probably depends, as Dr. @EdwardLoftus2 said. If dealing with someone who has failed other drugs and needed resections, [I’m] more inclined towards checking the level prior to the SC dose. In others where we have more room, [I] would check prior to SC dose.

EL: Agree—“are the stakes high?”

@IBDPharmacist: At this point, due to the cost of UST, most patients have already failed most other classes! [There] may be better outcomes if UST was used first line?!
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EVL: For sure. Go back to the NEJM paper; the results for the non-bio-failure pts in UNITI-2 were better than that for UNITI-1.

@ChrisAndersonM4: Do we have good data supporting drug monitoring for UST?

EVL: My take is we don’t know for sure yet. We are currently analyzing our own experience. One of the issues has been different assays, can we extrapolate, etc.

@IBDPharmacist: If no improvement at all after initial IV dose, [I] will check around 6 weeks after IV dose. If partial response, [I will check] UST level around 4 weeks, to see if [there is a] need to increase frequency to every 4 weeks. Waiting 16 weeks (for 2nd dose) is too long for most patients who remain symptomatic.

@GI_PhamD: What is the level cutoff you use at week 6 post-induction and the threshold for dose adjustment?

@IBDPharmacist: If partial response, check level 4 weeks after 1st SQ dose (mid-cycle).

@ShimaghavimiMD: This is why GITwitter and all of us should advocate NOW.

“With the increase of biologics to treat diseases like IBD, more and more patients with digestive diseases are subject to this policy.”
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EVL: Extensive disease for sure. For CD extensive SB disease, but in UC, don’t forget the protein-losing colopathy that (we think) occurs with extensive colitis.

@ptandonGI: In my opinion, maybe those with prior biologic failure, complicated disease (i.e., perianal CD, penetrating), numerous resections, extensive small bowel disease. Again, [we] still need to show that accelerated dosages help in this setting in order to prove the utility of proactive monitoring or re-induction with IV.

DC: [I] agree that these are patients I tend to do more proactive TDM with tumor necrosis factor inhibitors (TNFi)—but to a lesser extent with VDZ and UST; the limitation so far for me is (not) knowing what is the target level for these drugs during induction or maintenance.

EVL: Yes, what are the levels to act on? (And this gets into differences across assays) [It’s] still a bit confusing.

@QueirozNataliaF: IMHO, there is lack of data to support the use of proactive TDM for UST. Levels to target after induction depend on the desired outcome:

>6.9 normal FC

>11 endoscopic remission⁹
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**EVL:** Yes, it’s a rapidly evolving field!

**@ShimaghavimiMD:** There is a significant implementation with a growing gap due to lack of research [and] funding for research between pharmacometric research and pharmacotherapeutic practice, which in turn is crucial for therapeutic drug monitoring.

**@ShimaghavimiMD:** As we “The Who grew up with Nintendo and Sega genesis” grow and watch the evolution of artificial intelligence, I call on GITwitter IBDTwitter Meded to advocate for computer-assisted TDM rather than automatized TDM performed by computers.

**@IBDimmunology:** [It] may be silly on my part, but can we clarify “proactive?” To the ideologue, it means target pure trough level. To the pragmatist (e.g., me), it means trough—in the setting of an “objective” marker of inflammation. Didn’t @UofT_GI_Head gave a talk on this at CCCongress19?

**@UofT_GI_Head:** I did [g]ive a talk on this! Two years later, evidence in favor of proactive TDM is still fairly marginal. But checking drug levels just feels “do good,” no?

**@IBDimmunology:** I enjoyed and remembered your talk @UofT_GI_Head; it was one of the first talks I heard that challenged the notion of blind TDM.

**@pteryx:** Two ways to think of proactive TDM:
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a) changing biologics dose based purely on trough levels w/o clinical data,
b) changing biologics dose with trough levels and clinical data.

I don't think anyone will use (a) in practice.

As for (b),
b1) increasing dose to prevent loss of response in well patients,
b2) increasing dose to try to achieve remission in unwell patients.

I don't think there is good data for either, it's like a religion. [There is] better data for TNFi than [for] UST/VDZ though.

EVL: TDM is like US politics or religion! I think it’s another data point and you can’t be dogmatic about it. If you’re a dogmatist in IBD, patients will vote with their feet.

@ShimaghavimiMD: Many patients will for sure enjoy the visualization of circulating exposure incurred by their IBD medications, and an increasing number of them are keen to take the helm of self-monitoring—we need to innovate a better and faster route of TDM.

@UofT_GI_Head: Here is the study we should do: a pragmatic trial comparing the availability of drug levels to guide therapy versus just having clinical and biochemical indicators. I am not convinced the availability of quantitative drug levels drives better decision making.
@AsadurRahman87: I think this category of patient has the most to lose and therefore theoretically would provide the most sense to be more proactive.

@UofT_GI_Head: This paper does little to answer that question. Is the higher drug level driving the subsequent response or is a high drug level simply a marker of drug responsiveness? In other words, are drug levels the barometer or the weather?

So often clinicians confuse “predictive” with “actionable,” and “actionable” with “meaningful,” and “would” with “should;” i.e., if I knew the peak UST level, and it came back low, would/should I abandon ship? If I “act” by giving more UST the next day, does that matter?

SM: Great point @UofT_GI_Head! I think we can use this paper to generate a hypothesis that early concentration can be used to change dose, but [we] need a follow-up study to confirm that.

SM: Q4. In your experience, is drug level testing widely available and covered by insurance?

@ptandonGI: Not much of a problem in Canada, fortunately.

DC: [I] am always jealous of our Canadian friends—Maple syrup, Étè indien, and free healthcare! I have to say, I haven’t got much pushback checking levels for UST (using standard lab) but, again, I order it less often than TNFi level.
@vwaimieh: The patient support programs cover [the cost], but our public government insurance and hospitals won’t cover [the cost]—[I] wish we could order drug levels for our inpatients.

EVL: [It] hasn’t really been an issue at all. We use @mayocliniclabs.

@MahamHayatMD: Good point. [We] need to keep cost effectiveness in mind always. Also, in everyone’s experience, how long does it usually take for levels to be reported by the lab? Probably longer where it’s a send-out!

SM: [It] takes around a week to come back. I think it’s a send-out here. Recently, insurance approval has been easier for drug level testing for some reason.

@AsadurRahman87: In my experience, it is mostly covered or available with patient assistance from Prometheus.

@GI_PharmD: [I] have rarely received notice from patients or payors that drug levels are not covered and require a clinical appeal to be covered. If using Prometheus, I do counsel on potential out-of-pocket cost and confirm if [it is] a concern for patients.

@ChrisAndersonM4: Do insurance companies care about the drug levels for approving dose changes?
Discussion Summary

**DC:** It can be a double-edge result, @ChrisAndersonM4. Specially with @waqqasafif group experience of patients responding to extra IV dose even when they had an adequate drug level at baseline.

**@GI_PharmD:** I have seen a few denials for dose escalation despite providing symptoms and objective markers information due to request for UST level, even though this isn’t a standard-of-care practice everywhere.

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**SM:** *Q5. What would you do if you have a low drug level and no/partial/loss of response during maintenance therapy?*

On the poll, 61.1% of 36 respondents chose to increase the frequency of UST to every four weeks, 11.1% elected to give an extra IV dose, another 11.1% decided to switch to a different drug, and 16.7% were unsure of what to do.

**@PerelmansPearls:** I’d go every 6 weeks [and] see if helps.

**@UofT_GI_Head:** What is the level of evidence that dose optimization = disease optimization? When it comes down to it, we know so little about why anyone, at any time, loses the response to therapy.

**@ChrisAndersonM4:** Has IV been the only therapy studied for Stelara in CD?
**Discussion Summary**

**DC:** I typically give another IV dose (often easier/faster to get approved than a change in SC frequency) and decrease the SC interval, like @EdwardLoftus2. However, I have to say, it’s been harder to get approval recently for every 4–6 week UST.

@**elrets:** Given the cost of UST in the Panama, reactive TDM makes sense if [there is] no/partial response (adequate levels $\rightarrow$ change prescription rather than increase to every 4 weeks).

Applying available data to regional “circumstances,” [it is] yet another challenge in managing our IBD patients.

@**joshsteinbergMD:** [I] agree, @DCharabaty—even in the last two months I’ve had to appeal several denials for changing from every 8 to 4 or 6 weeks. Reaching for IV dose instead can definitely be a more practical approach.

@**ShimaghavimiMD:** Transitioning from IV to SC administration can offer distinct cost advantages to payers. Many SC medications do not require premedication, resulting in direct cost savings. The caveat is to make sure the payer knows about safety and efficacy.

Explain to the payer regarding treatment adherence and safety with IV versus SC formulations.
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According to Zdovc et al. (2021)\textsuperscript{12}, their findings could be used to guide stratified UST treatment in CD, particularly in patients with unfavorable characteristics who might benefit from early transition to 4-weekly maintenance dosing.

**EVL:** Most often, [I] increase the frequency of SQ to every 4–6 weeks. If already on every 4 weeks and other options [are] limited, [I] will add an IV load.

**SM:** [I] haven’t done reinduction with IV before. [Are there] any issues with insurance approval? [Should you] keep them on an every-4-weeks SQ regiment afterwards?

**EVL:** The cost of the IV (“$ per mg”), last I checked, was much lower than SQ—so generally less insurance pushback.

**@IBDPharmacist:** The cost of IV << SQ, and dose is weight based; [it] would have been useful to have studies to support IV dosing for maintenance in a select population. [Are there] any studies out there?

**EVL:** Not aware of any with purely IV.

**@ijlalakbar:** How much of that is allowed by insurance? How do you navigate that elephant in the room?

**EVL:** Be the elephant!
SM: Q6. Based on this study, would you proactively make a change to the treatment if the patient has a low drug level at week 2 after IV UST?

On the poll, 41.7% of 24 voters chose no or were not sure, 33.3% elected to give an extra IV dose at week 4, and 25% planned for SQ dose every four weeks.

DC: Based [on] this study, I might be inclined to move the first SQ dose at week 4. However, recently, I have been having a hard time getting every-4-weeks dosing approved. But if the same principle of “hit hard early to get results” applies to UST like it does to TNFi, nail it!

EVL: If that level was less than 20 mcg per mL, then maybe yes, escalate early to every 4 weeks.

@AsadurRahman87: [I] would probably choose the additional IV dose because of the relative ease to get it approved on time compared to SQ. And also, because based on this paper, the patient getting the drug level checked this early is someone who is probably high risk and doesn’t have time on their hands.

@ShimaghavimiMD: In patients not achieving remission with standard dosing at week 16, transition to 4-weekly SQ maintenance dosing with or without IV reinduction resulted in comparably higher remission rates at week 32 (51.1% vs. 49.2%).¹²
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Now, according to Yao et al. (2021)\textsuperscript{13}, patients with a UST concentration $>1.12 \mu g/mL$ had a significantly higher rate of endoscopic remission than those without (70.0\% vs. 11.1\%, $P = 0.02$).

@PerelmansPearls: I went from fighting with insurance every 6 months [to] now looking like 3 months even for every 6.

@ShimaghavimiMD: We need to start collecting data on each conversation and end point for each insurance companies. Share it with the group. Create a super force of influencers and advocate on daily basis. Whenever you have free time, call the insurance company and remind them again and again.

@PerelmansPearls: I think we are doing that with daily prior authorizations, from medications to screening at 45. You’d think we’re dentists with all the teeth pulling!

@ShimaghavimiMD: Yes, I understand. What if we just shared what we discussed with each unique insurance company on how we got the prior authorization, made a report, and published it. No patient name, just case and how the prior authorization was approved (transcript).

@PerelmansPearls: @CrohnsColitisFn\textsuperscript{14} has something like that to help us out. Not sure if you’ve seen it, but [it is] pretty useful.

@ShimaghavimiMD: \textsuperscript{15}
Conclusion

Hanzel et al.\textsuperscript{1} concluded that early measurements of serum UST concentrations might be used to optimize treatment for CD. This prospective study found that serum UST concentrations measured within the first two weeks, and within as early as 1 hour after IV infusion could be used to identify patients most likely to achieve endoscopic remission. However, it is unknown if more frequent dosing in patients with a low drug level will lead to a higher response rate. Prospective randomized studies are needed to answer this question. Based on this study, the experts concluded that in a select group of high-risk patients, a very low concentration might be an appropriate indication to increase dosing frequency.
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References


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