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**Observations and Research**

# Serum Ustekinumab Concentrations Are Associated With Remission in Crohn's Disease Defined by a Serum-Based Endoscopic Healing Index

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**Background:** Optimal ustekinumab levels (UST) in Crohn disease (CD) treatment have not been defined. We set out to define the optimal UST to differentiate between remission and active CD, as defined using the serum-based endoscopic healing index (EHI).

**Methods:** Paired serum UST and EHI tests were analyzed. Remission was defined as EHI <20. Active disease was defined as EHI ≥50. The proportion of patients in remission was compared across UST quartiles. UST in subjects with EHI <20 and EHI ≥50 were compared. An area under receiver operating characteristic curve was generated to identify an optimal UST to differentiate between active disease and remission.

**Results:** A total of 337 unique patients were identified; median UST and EHI were 5.0 µg/mL [interquartile range (IQR) 2.7–9.1] and 37 (IQR 26–53), respectively. EHI <20 (remission) was found in 57 (16.9%) patients. EHI ≥50 (active disease) was found in 97 (28.8%) patients. Higher proportions of subjects were in remission for increasing UST quartiles, $P = 0.01$. Median UST in patients with EHI <20 and EHI ≥50 were 7.5 µg/mL (IQR 4.6–10.9) and 3.1 µg/mL (IQR 1.8–6.6), respectively, $P < 0.001$. An UST threshold of 3.75 µg/mL optimally differentiated between active disease and remission (area under the curve 0.725). UST levels >3.75 µg/mL were associated with a lower proportion of subjects with active disease (EHI ≥50; 18.9%) compared with UST levels ≤3.75 µg/mL (45.6%, $P < 0.001$).

**Conclusions:** Using the EHI, we identified a threshold UST level of 3.75 µg/mL to optimally differentiate between active and quiescent CD. These data suggest that UST serum concentrations of >3.75 µg/mL are optimally associated with endoscopic remission in CD.

## Lay Summary

We used a blood test to determine whether patients with Crohn's disease had active disease. We compared ustekinumab drug levels between patients with active and inactive disease. Patients with a drug level >3.75 µg/mL were more likely to have inactive disease.

**Key Words:** Crohn disease, ustekinumab, endoscopic healing index, therapeutic drug monitoring

## Introduction

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract.[1] It is associated with significant morbidity and health resource utilization, and its prevalence is increasing globally.[2–4] Starting with the approval of infliximab, biologic drugs have represented a cornerstone of inflammatory bowel disease (IBD) treatment for the past 2 decades.[5] Among the most impactful advances in our use of biologics in that time are (1) the use of therapeutic drug monitoring (TDM) and (2) the advent of novel biologic agents such as ustekinumab; a fully human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity to the p40 subunit of interleukin (IL)12 and IL-23.[6,7] Widespread adoption of TDM for anti-TNF drugs in the treatment of IBD has been fueled by 3 key factors: the widespread availability of TDM assays, the realization that higher anti-TNF drug concentrations are associated with improved clinical, biochemical, and endoscopic outcomes, and the identification of optimal target drug concentrations.[7–11]

Ustekinumab was approved by the FDA for the treatment of moderate to severe Crohn disease in 2016 following demonstration of safety and efficacy in the UNITI and IM-UNITI trials.[6] In 2019, it was approved for the treatment of moderate to severe ulcerative colitis.[12] Assays for ustekinumab TDM are now commercially available. Additionally, the literature to date supports an association between higher drug concen-

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trations and better disease outcomes.[13–17] However, a relative paucity of data to identify optimal target ustekinumab concentrations has limited the utility of ustekinumab TDM in clinical practice. To date, studies attempting to identify target ustekinumab concentrations have been limited either by small numbers, or the use of (post hoc analysis of) clinical trial data, which may not be representative of "real world" practice.

Until recently, the use of surrogate markers of endoscopic activity in Crohn's disease has been limited to C-reactive protein (CRP) and fecal calprotectin. CRP correlates poorly with endoscopic activity.[18,19] Sensitivity of fecal calprotectin is better than CRP, but sensitivity may vary by disease location, and lower patient acceptability of stool tests limits its utility in "real world" research.[3,19,20] Such limitations of existing biomarkers led to the recent development of the serum-based endoscopic healing index (EHI) (Monitr TM). This test is validated against endoscopy in adult patients with Crohn's disease. Measurement of 13 protein biomarkers (ANG1, ANG2, CRP, SAA1, IL7, EMMPRIN, MMP1, MMP2, MMP3, MMP9, TGFA, CEACAM1, and VCAM1) is used to generate an EHI score of 0–100. An EHI of <20 rules out endoscopic disease activity with a sensitivity of 83%–97%, whilst an EHI ≥50 rules in active disease with a specificity of 88%–100%. For EHI values between 20 and 50, specificity for ruling in active disease progressively increases with increasing EHI.[21]

The objective of our study was to define the optimal ustekinumab concentration to differentiate between active inflammation and remission in Crohn's disease, using the serum-based EHI.

## Materials and Methods

Data were extracted for results of ustekinumab serum concentrations and EHI tests from a cohort of samples submitted for analysis to a commercial clinical laboratory accredited by the American College of Pathologists (Prometheus Biosciences, San Diego, CA). All personal information was removed to protect privacy. All subject data were deidentified and all Health Insurance Portability and Accountability Act (HIPAA) identifiers were removed prior to extraction from the clinical laboratory database. The data set was maintained with no possibility of identification of personal information.

Subjects meeting the following inclusion criteria were included for analysis: (1) age ≥18 years; (2) ustekinumab concentration tests and EHI tests performed within 30 days of each other; (3) results of both tests reported on or before August 31, 2019. Ustekinumab concentration tests and EHI tests were performed at the discretion of the treating physician. Timing of these tests in relation to ustekinumab dosing cannot be confirmed. Subjects were excluded if ICD codes for ulcerative colitis were indicated on any order for either test. Ustekinumab serum drug measurements were performed using the Anser platform, which is a drug-tolerant, homogenous mobility shift assay. The lower limit of quantitation for ustekinumab using this assay is 0.9 µg/mL, and the upper limit of quantitation is 25 µg/mL. The lower limit of quantitation for antibodies to ustekinumab is 1.6 U/mL, and the upper limit of quantitation is 100 U/mL. To provide the most robust analysis, extremes of the EHI were utilized as these scores are most clearly correlated with endoscopic outcomes. In keeping with previously validated EHI thresholds, remission was defined as EHI <20 (83%–97% sensitivity for ruling out endoscopic active disease) and active inflammation was defined as EHI ≥50 (88%–100% specificity for ruling in endoscopic active disease).[21]

In order to ascertain presence of an exposure–response relationship, chi-square test was applied to establish whether the proportion of Crohn's disease patients (1) in remission (EHI <20) and (2) with active disease (EHI ≥50), differed across ustekinumab concentration quartiles. We also compared EHI values across ustekinumab concentration quartiles using Kruskal–Wallis test.

Ustekinumab concentrations in subjects with (1) EHI <20, (2) 20 ≤ EHI <50, and (3) EHI ≥50 were compared using Kruskal–Wallis test, and subsequent Mann–Whitney *U* test. An area under receiver operating characteristic curve was generated to identify an optimal ustekinumab concentration (using Youden index) to differentiate between patients in remission (EHI <20) and those with active disease (EHI ≥50). We compared the proportion of patients in remission (EHI <20) and with active disease (EHI ≥50) among those with an ustekinumab concentration above and below the optimal threshold using Fisher exact test. Statistical analysis was performed using R version 3.6.1. For all analyses, a $P$ value <0.05 was considered significant.

## Ethical Considerations

National Institutes of Health criteria for exemption from human subject's regulations (category 4) were met as all personal information was removed from the data set to protect privacy. Data extraction was reviewed and approved by the Prometheus Biosciences privacy office for compliance.

## Results

### Patient Characteristics

We identified 337 unique patients with paired ustekinumab serum concentrations and EHI results (drawn within 30 days of each other): median age was 42 years [interquartile range (IQR) 32–56] and 140 (41.5%) were males. For 308 (91.4%) patients, ustekinumab concentrations and EHI were tested on the same sample. Ustekinumab dosing information was available for 169 (50.1%) patients. Of these, 138 (81.7%) were on standard dosing of 90 mg every 8 weeks, 10 (5.9%) were on 90 mg every 6 weeks, and 21 (12.4%) were on 90 mg every 4 weeks. (The nature of our study precluded availability of information regarding disease phenotype or prior IBD therapies.) Median ustekinumab concentration was 5.0 µg/mL (IQR 2.7–9.1) and median EHI was 37 (IQR 26–53). An EHI <20, signifying remission was found in 57 (16.9%) patients. An EHI ≥50 signifying active Crohn disease was found in 97 (28.8%) patients. (The remaining 183 (54.3%) subjects had an EHI between 20 and 50.)

### Serum Ustekinumab Concentrations vs EHI

Quartile analysis of serum ustekinumab concentrations showed an exposure–response relationship, with an increasingly higher proportion of subjects in remission (EHI <20) across quartiles 1, 2, and 3, $X^2$ 11.255, $P$ = 0.01 (Fig. 1A). The proportion of patients in remission in quartiles 1, 2, 3, and 4 was 5/85 (5.9%), 14/84 (16.5%), 19/84 (22.4%), and 19/84 (22.4%), respectively. Similarly, the proportion of patients with active disease (EHI ≥50) was progressively lower across ustekinumab concentration quartiles 1, 2, and 3, $X^2$ 21.718, $P$ < 0.001 (Fig. 1B). The proportion of patients with active disease in quartiles 1, 2, 3, and 4 was 41/85 (48.2%), 21/84 (25.0%), 16/84 (19.0%), and 19/84 (22.6%), respectively. Median EHI across

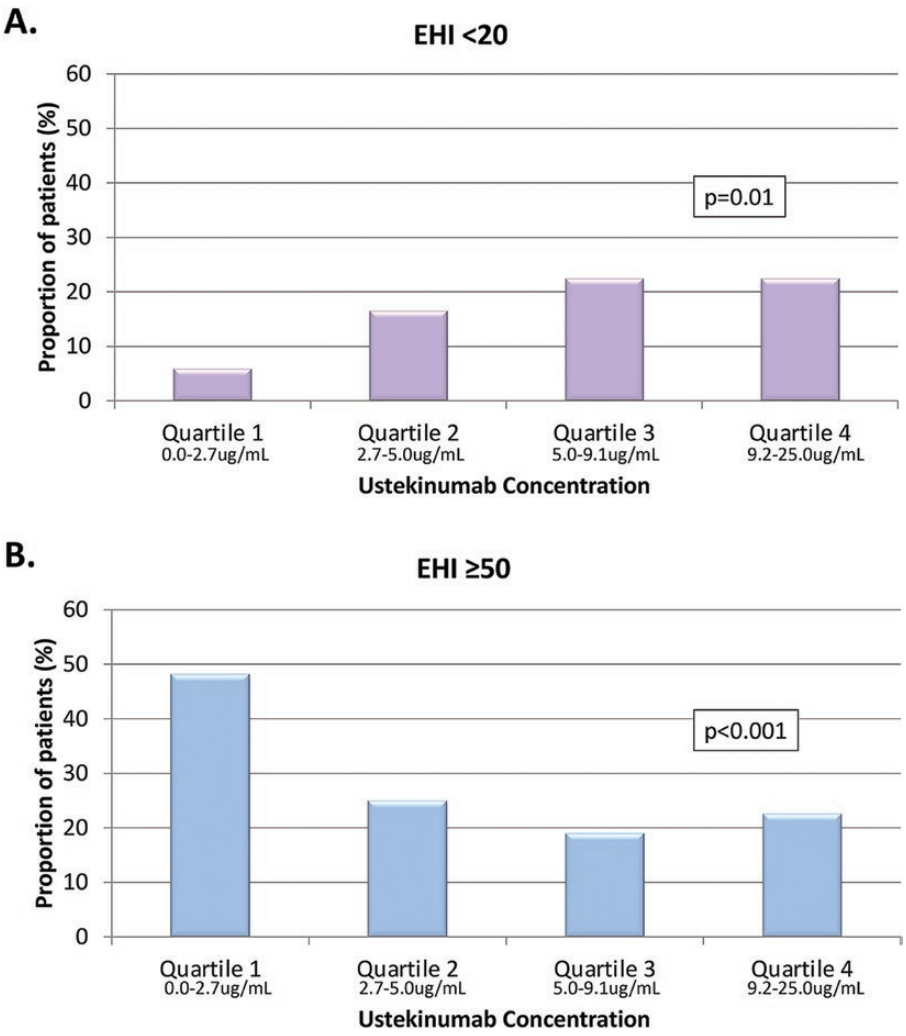


**Figure 1.** (A) Proportion of patients in remission across ustekinumab concentration quartiles as defined by EHI <20. (B) Proportion of patients with active disease across ustekinumab concentration quartiles as defined by EHI ≥50.

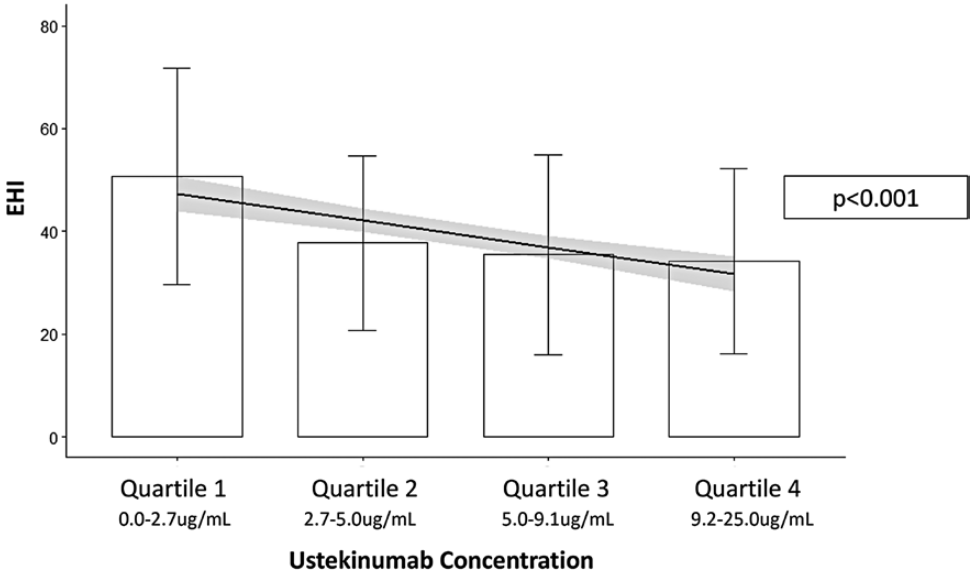


**Figure 2.** EHI is progressively lower across ustekinumab concentration quartiles.

ustekinumab concentration quartiles 1, 2, 3, and 4 were: 49 (IQR 36–64), 36 (IQR 26.8–48.8), 34 (IQR 22.5–42), and 31.5 (IQR 20.8–49), respectively, $P < 0.001$ (Fig. 2).

Median ustekinumab concentrations in patients with (1) EHI <20, (2) 20 ≤ EHI < 50, and (3) EHI ≥50 were 7.5 µg/mL (IQR 4.6–10.9), 5.2 µg/mL (IQR 3.0–9.15), and 3.1 µg/mL (IQR 1.8–6.6), respectively, $P < 0.001$ (Fig. 3). Ustekinumab concentrations were significantly higher in patients with EHI <20 (remission) vs patients with EHI ≥50 (active disease), $P < 0.001$.

### Optimal Ustekinumab Concentration to Differentiate Between Remission and Active Crohn Disease as Defined by EHI

Area under receiver operating characteristic curve analysis identified an ustekinumab concentration threshold of 3.75 µg/mL to optimally distinguish between remission and active Crohn's disease (ie, EHI <20 vs EHI ≥50); area under the curve 0.725 [95% confidence interval (CI) 0.644–0.805], specificity 0.842 (95% CI 0.5789–0.9123), and sensitivity 0.588 (95% CI 0.3918–0.701) (Fig. 4). Of 212 patients with ustekinumab concentrations >3.75 µg/mL, 48 (22.6%) were in remission (EHI <20), in comparison to 9 (7.2%) of 125 patients with ustekinumab concentrations ≤3.75 µg/mL, $P < 0.001$. Active disease (EHI ≥50) was evident in 40 (18.9%) patients with an ustekinumab concentration >3.75 µg/mL, in comparison to 57 (45.6%) of 125 patients with an ustekinumab concentration ≤3.75 µg/mL, $P < 0.001$ (Fig. 5).

### Antibodies to Ustekinumab

Antibodies to ustekinumab were detected in 3 (0.9%) patients. One patient with antibody levels of 24.0 U/mL had undetectable drug and an EHI of 40. Anti-ustekinumab antibody levels in the other 2 patients were 2.5 U/mL (ustekinumab concentration 1.9 µg/mL) and 8.8 U/mL (ustekinumab concentration 9.2 µg/mL). EHI in these patients was 47 and 6, respectively.

## Discussion

Whilst our armamentarium of biologic treatments for Crohn's disease has expanded significantly in recent years, it

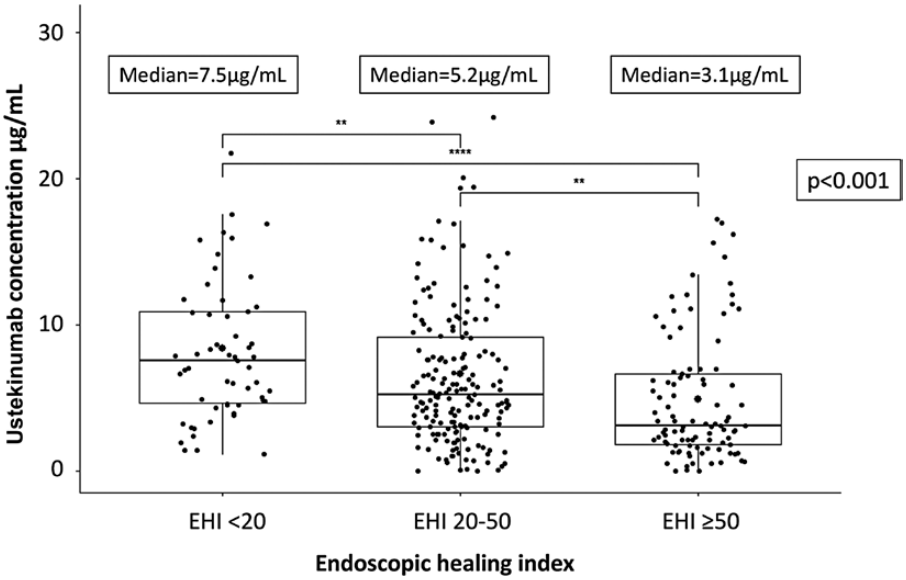


**Figure 3.** Ustekinumab concentrations according to EHI.

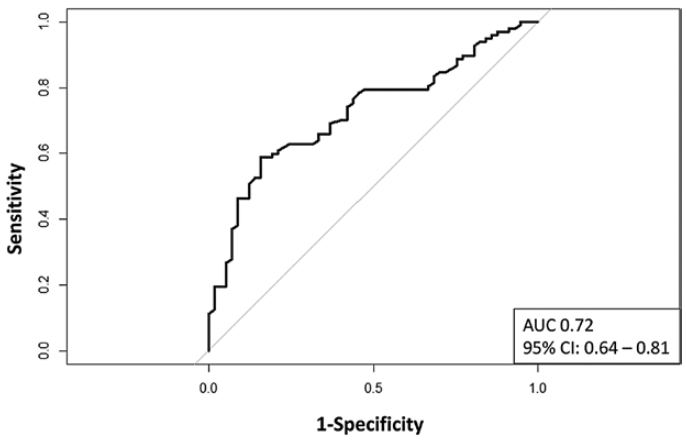


**Figure 4.** Area under receiver operating characteristic (AUROC) curve analysis identifies an optimal ustekinumab level of 3.75 µg/mL to differentiate between active and inactive Crohn disease.

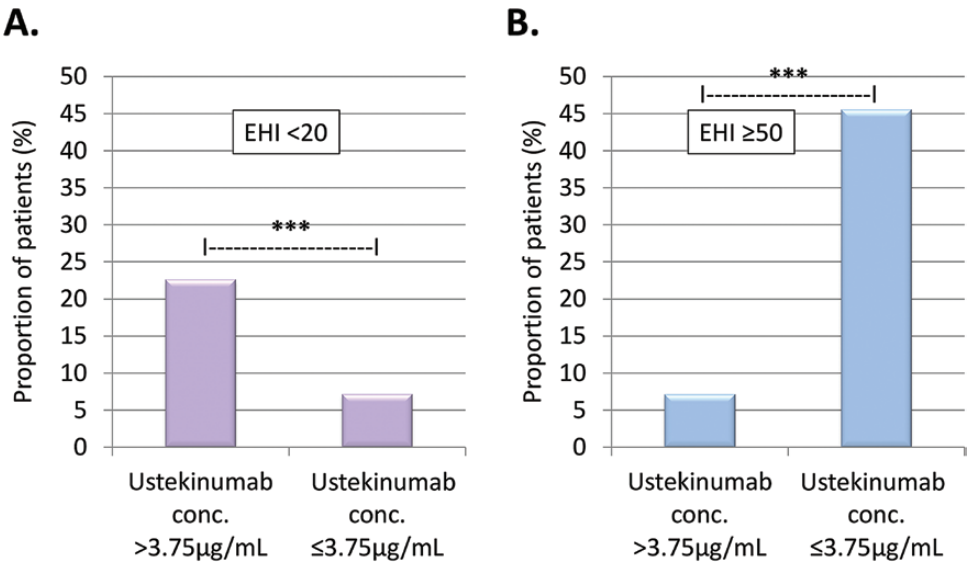


**Figure 5.** Proportion of patients with (A) EHI <20 and (B) EHI ≥50 according to ustekinumab concentration above or below 3.75 µg/mL. ***$P < 0.001$.

remains limited by the lack of efficacy of these treatments in a substantial proportion of patients.[5] Widespread experience with anti-TNF TDM has demonstrated its utility in maximizing treatment efficacy, as well as improving cost-effectiveness, and assessing patients with loss of response.[5,7,22–25] Successful utilization of ustekinumab TDM requires that we establish target drug concentrations. Our study contributes significantly to this process by examining the association between ustekinumab concentrations and validated measures of Crohn disease endoscopic activity.

We identified an ustekinumab concentration of 3.75 µg/mL to optimally differentiate between remission and active Crohn's disease, as defined using a novel serum-based marker of endoscopic inflammation. The EHI has been validated in 2 separate patient cohorts. Using an EHI cutoff of <20, EHI has a sensitivity of 83%–97% to rule out endoscopically active Crohn disease (defined as total SES-CD >2 and/or SES-CD ≥2 in 1 bowel segment). The specificity of EHI in detecting endoscopically active disease is 88%–100% using a cutoff of EHI ≥50.[21] Use of these strict, validated cutoffs to define remission and active Crohn disease contributes to the robustness of our study. Importantly, the EHI performs well across Crohn disease phenotypes, as stratified by disease location (ileal, ileocolonic, colonic) and disease behavior (inflammatory, stricturing, penetrating).[21] Additionally, sensitivity and specificity for active disease using the described thresholds are similar among biologic-naive and biologic-experienced cohorts; sensitivity of 97.1% and 83.2%, specificity of 100% and 87.8% among biologic-naive and biologic-experienced cohorts, respectively.

The 3 largest studies to date identifying threshold ustekinumab concentrations related to treatment response in Crohn disease are that of Adedokun et al, Battat et al, and Verstockt et al.[13–15] Adedokun et al performed a post hoc analysis of data from the UNITI and IM-UNITI studies.[14] They reported that trough concentrations above 0.8–1.4 µg/mL are associated with higher rates of clinical remission (as defined by Crohn's Disease Activity Index (CDAI) <150) at week 24 of maintenance treatment. This is markedly lower than our identified threshold of 3.75 µg/mL. There are several possible explanations. Firstly, in IM-UNITI, half of patients receiving ustekinumab were given 90 mg every 12 weeks. Maintenance trough concentrations were 3 times higher in patients on 8 week dosing.[6] Thus, the 12 week dosing arm would have significantly driven down average trough concentrations across the study population. Secondly, our definition of inactive disease was much more stringent than that of Adedokun et al. We adopted validated EHI cutoffs with high sensitivity and specificity for endoscopic inflammation. By contrast, CDAI has poor correlation with endoscopic inflammation in Crohn disease.[26,27] Thirdly, Adedokun et al used a different assay (electrochemiluminescent immunoassay) that is not clinically available.

In a single-center retrospective study of 62 patients, Battat et al reported an ustekinumab concentration threshold of 4.5 µg/mL to optimally distinguish between patients with and without endoscopic response after a minimum of 6 months treatment.[13] This is somewhat higher than our identified threshold of 3.75 µg/mL. There are 2 likely reasons for this. Firstly, the majority of patients in the study of Battat et al were receiving ustekinumab at a dosage of 90 mg every 4 weeks. By contrast, over 80% of patients in our study for whom ustekinumab dosing was available were on 90 mg every 8 weeks. Secondly, all of the patients in the study of Battat et al were anti-TNF experienced. Anti-TNF experienced patients are more refractory to ustekinumab treatment, and thus may require higher drug concentrations to achieve therapeutic benefit.[6] Our study validates the findings of Battat et al, who utilized the same commercially available assay, by demonstrating that higher thresholds to those outlined by Adedokun et al are needed in order to achieve better objective biomarker and endoscopic outcomes.

Verstockt et al performed a single-center prospective study of 86 patients using a sandwich-type ELISA.[15] A week 24 ustekinumab concentration of 1.9 µg/mL was deemed to represent the minimal drug exposure required to maximize likelihood of endoscopic response (assessed at week 24), with a negative predictive value of 85.2%. However, low specificity

and positive predictive values (of 53.7% and 34.2%, respectively) suggest that ustekinumab concentrations required to achieve endoscopic response were higher than 1.9 µg/mL in a substantial proportion of patients.

Several studies have described enhanced treatment efficacy with ustekinumab dose intensification. In the IM-UNITI ustekinumab maintenance study, patients who failed to respond to 90 mg every 12 weeks had their dosing interval shortened to every 8 weeks. Sixteen weeks following dose intensification, 41.4% were in clinical remission, and 55.2% had clinical response.[6] Ollech et al recently described a retrospective, single-center experience of ustekinumab dose intensification.[28] At physician discretion, 110 patients who were initially treated with 90 mg every 8 weeks were prescribed 90 mg every 4 weeks. Assessment following dose escalation showed lowering of Harvey Bradshaw Index scores, CRP, and fecal calprotectin. In their multicenter retrospective study of 142 patients who underwent ustekinumab dose escalation (by means of dose interval shortening and/or IV reinduction), Kopylov et al reported clinical response in over 50% of patients.[29] All of these studies utilized empiric dose intensification strategies, which were not guided by ustekinumab concentrations, and no studies to date have examined the role of ustekinumab concentrations in determining the success of dose intensification strategies. Importantly, ustekinumab dose intensification and/or higher ustekinumab concentrations do not appear to be associated with increased risk of adverse events.[14,28,29]

Our study has a number of strengths. Firstly, we used a validated objective serum-based marker of endoscopic disease activity. The EHI reflects endoscopic activity in Crohn disease more accurately than CRP or clinical scores. Unlike fecal calprotectin, its performance is not affected by disease location.[20,21] Secondly, our assessments of ustekinumab concentrations and EHI were closely temporally related, with over 90% of subjects having both ustekinumab concentrations and EHI tested on the same sample. Thirdly, to our knowledge, this is the largest "real world" cohort to date looking at the association between ustekinumab concentrations and Crohn disease activity. Fourthly, study subjects were from a large number of different centers across North America. This adds to the generalizability of our findings.

We must also acknowledge the limitations of our study. Firstly, we have no way of confirming that ustekinumab concentrations were trough concentrations. Secondly, the nature of our study precluded acquisition of clinical details such as disease phenotype, disease duration, time since starting ustekinumab, use of other medications and endoscopy data. With regard to time since starting ustekinumab, post hoc analysis of IM-UNITI study data shows that ustekinumab concentrations reach a steady state by the second maintenance dose.[14] Thus, we would not expect variation in ustekinumab concentrations secondary to differences in therapy duration. With regard to use of other medications, concomitant use of immunomodulators such as azathioprine and methotrexate do not impact ustekinumab concentrations or efficacy.[14] However, some patients may have been on other medications such as steroids. Had information regarding disease phenotype and prior biologic use been available, we could have stratified our analysis according to these findings. Crohn disease is more refractory to ustekinumab in the setting of prior anti-TNF use. Thus, such patients may require higher drug concentrations.[6] Therapeutic drug concentrations may also vary depending on disease phenotype, as has been suggested to be the case for infliximab.[30]

## Conclusions

Our study adds to a growing body of evidence demonstrating a clear exposure–response relationship regarding ustekinumab treatment in Crohn disease. Using the novel, validated serum-based EHI, we identified a threshold ustekinumab concentration of 3.75 µg/mL to optimally differentiate between active and quiescent Crohn disease. These real-world data, which use a commercially available TDM assay, suggest that therapeutic drug concentrations initially proposed following post hoc analysis of ustekinumab clinical trials are too low.

We advocate for prospective randomized controlled trials to ascertain the potential therapeutic benefit of adjusting dosing strategies to achieve target ustekinumab concentrations.

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## Funding

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## Conflict of Interest Statement

M.W.: honoraria received from Takeda and PrecisionBiotics. K.B. and R.B.: no COI to declare. D.H. has served as a consultant for Janssen, BMS, AbbVie, Pfizer, Takeda, and Samsung. D.W. has served as a speaker, consultant, and received clinical research support from Janssen. He has also served as a consultant for Prometheus. L.O. and A.J. are employees of and owns stock options for Prometheus Biosciences. M.S. has received research support from Prometheus laboratories. He has received research support from, and served as speaker and consultant for Janssen, AbbVie, Takeda, Pfizer, and Gilead.

## Author Contributions

M.W.: data interpretation, drafting of original manuscript, and manuscript revisions. K.B.: data analysis and data interpretation. R.B., D.H., and D.W.: data interpretation and critical revision of manuscript. L.O.: data analysis and critical revision of manuscript. A.J.: study concept, data analysis, provision of raw data, and critical revision of manuscript. M.S.: study concept. Main supervisor regarding data analysis, data interpretation, and critical revision of manuscript.

## Data Availability

Data available on request due to privacy/ethical restrictions.

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