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Association of golimumab trough concentrations during maintenance with clinical, biological, endoscopic and histologic remission in patients with ulcerative colitis

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Summary

Background: Optimal thresholds for golimumab concentrations during maintenance for important outcomes are lacking.

Aim: The aim of the study was to investigate the association of golimumab trough concentrations during maintenance with key outcomes, including endoscopic and histologic remission, and long-term event-free persistence with golimumab, in patients with UC.

Methods: This multicentre, cross-sectional study included UC patients on golimumab maintenance recruited either in remission or during a flare. Colonoscopy was scheduled, and study-specific rectocolonic biopsies were taken for blind central histologic reading. Samples for golimumab trough concentrations were collected close to colonoscopy.

Results: Fifty-two patients were included. Median golimumab trough concentrations (μg/ml) were significantly higher in patients who had clinical remission (2.01 vs. 0.72, $p = 0.047$), combined clinical-biochemical remission (PMS ≤2 + faecal calprotectin <250 μg/g) (2.21 vs. 1.47, $p = 0.041$), endoscopic healing (Mayo endoscopic subscore 0) (2.52 vs. 1.47, $p = 0.003$), histologic remission (Geboes index ≤2.0) (2.33 vs. 1.50, $p = 0.02$) and disease clearance (clinical remission endoscopic healing + histologic remission) (2.52 vs. 1.70, $p = 0.009$), compared with those not meeting these criteria. Golimumab concentrations were significantly higher in patients who avoided golimumab dose escalation/discontinuation during follow-up (2.24 vs. 0.98, $p = 0.012$). Receiver-operating characteristic analyses identified golimumab thresholds [area under the curve] of 0.85 [0.76], 1.90 [0.76], 2.29 [0.75], 1.79 [0.68], 2.29 [0.72] and 1.56 [0.71] μg/ml as associated with clinical remission, combined remission, endoscopic healing, histologic remission, disease clearance and long-term event-free persistence with golimumab, respectively.

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Conclusions: Golimumab trough concentrations during maintenance are associated with favourable treatment outcomes including endoscopic healing, histologic remission and long-term persistence on golimumab. We identified the optimal golimumab thresholds most closely associated with key outcomes.

1 | INTRODUCTION

Biologics and targeted small molecules have changed the goals of ulcerative colitis (UC) therapy, with the focus now on preventing disease progression rather than just controlling symptoms. The PURSUIT studies have demonstrated that golimumab, a human monoclonal anti-TNF agent, was effective for induction and maintenance of remission and mucosal healing in patients with ulcerative colitis (UC).[1,2] According to the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) 2 consensus, endoscopic healing together with symptomatic remission (termed deep remission) are considered the main goals in UC.[3] However, histologic remission represents an important objective outcome distinct from endoscopic healing in UC and is associated with lower risks of hospitalisations, colectomy and colorectal cancer.[4–6] Therefore, an even more stringent treatment target called 'disease clearance', which is essentially a combination of clinical, endoscopic and histologic remission, has been recently proposed as the ultimate therapeutic goal for UC.[7]

Reactive therapeutic drug monitoring (TDM) of anti-TNF agents may help identify mechanisms of loss of response and guide the selection of the optimal intervention in individual patients and has been shown to be cost-effective compared with empiric dose escalation.[8,9] Proactive TDM showed that anti-TNF trough levels are correlated with clinical response, clinical remission and endoscopic healing in patients with inflammatory bowel disease (IBD).[10,11] Conversely, inadequate drug concentrations and antidrug antibodies are associated with poor clinical outcomes.[12,13] Infliximab trough concentrations during maintenance therapy are associated with endoscopic and histologic healing in UC patients, with higher levels of infliximab being necessary to achieve increasingly stringent therapeutic goals.[14]

Post hoc analysis of the PURSUIT trials demonstrated a positive association between serum golimumab trough concentrations (SGC) and efficacy outcomes, including endoscopic healing, during both induction and maintenance for UC.[15] However, real-world data on the optimal SGC threshold during maintenance for important outcomes like endoscopic healing and histologic remission are lacking, and the use of golimumab TDM has been limited in clinical practice, even though SGC monitoring is now feasible in many centres.[16] The aim of this study was to investigate the exposure–response relationship of serum golimumab trough concentrations during maintenance therapy with outcomes, including endoscopic healing and histologic remission, in patients with UC. Additionally, we aimed to identify SGC thresholds most closely associated with key outcomes. We also assessed the predictive value of SGC for long-term outcomes such as golimumab dose escalation-free survival and golimumab discontinuation-free survival.

2 | METHODS

2.1 | Study design and patient population

This was a multicentre, cross-sectional cohort study of UC patients treated with golimumab. The eligible population included patients aged ≥18 years with an established diagnosis of UC who had received at least five maintenance doses of golimumab prior to inclusion. The study population consisted of consecutive patients from each centre who were scheduled for colonoscopy according to clinical practice. Patients underwent colonoscopy either for surveillance of dysplasia, for assessment of disease activity in patients with IBD-related symptoms or to evaluate mucosal healing based on a treat-to-target strategy for patients in clinical remission. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies were used in the design of the study and the preparation of the manuscript.[17]

2.2 | Study procedures

Samples for golimumab trough concentrations and anti-golimumab antibodies (AGA) were taken the day of the scheduled subcutaneous golimumab administration closest to the colonoscopy (within 2 weeks before or after the procedure) (Figure S1). Samples for C-reactive protein (CRP) and faecal calprotectin (FC) were obtained on the day of the extraction of SGC. Clinical activity was evaluated using the partial Mayo score (PMS). To assess Health-Related Quality of Life (HRQoL), patients completed two validated questionnaires: the generic European Quality of Life-5 Dimensions (EQ-5D) and the disease-specific Spanish version of the Short Inflammatory Bowel Disease Questionnaire (SIBDQ). The EQ5D index score ranges from −0.654 to 1.000, where higher scores indicate better HRQoL.[18] The EQ-5D also includes a 100-point VAS, where 0 represents the worst imaginable health state and 100 the best imaginable one. SIBQD was developed and validated specifically for IBD patients and has shown excellent correlation with IBDQ-32.[19,20] SIBDQ includes 10 questions assessing the effect of IBD on social, emotional and physical well-being. The overall score was obtained by summing up each item score and the result was transformed into a 0–100 scale, where 0 represents the worst health state.

The centrally monitored endoscopic activity was scored using the Mayo endoscopic subscore (MES). In addition to routine

biopsies for surveillance of dysplasia, if indicated, a study-specific biopsy protocol was implemented. During colonoscopy, two rectal biopsies (denoted R-biopsy) and two sigmoid biopsies (denoted S-biopsy) were taken. In patients with maximum endoscopic activity beyond the sigmoid colon, two additional biopsies of this area of activity were taken. In order not to break the blind of pathologists, in these patients, only biopsies of the rectum (R-biopsy) and biopsies of the area with the highest endoscopic involvement (denoted S-biopsy—replacing the sigmoid biopsy) were submitted blinded to the patient symptomatic and endoscopic activity for central histologic reading in the leading centre. Biopsies were evaluated by two independent gastrointestinal pathologists using the Geboes index.[21] The biopsy with the maximum histologic activity was selected to grade the histologic score. Disagreements were resolved by discussion or with the intervention of a third pathologist.

2.3 | Measurement of golimumab trough concentrations and anti-golimumab antibodies

SGC and AGA were determined centrally in the leading centre using an enzyme-linked immunosorbent assay (ELISA) (LISA-TRACKER Golimumab, Theradiag, France) according to manufacturer instructions. The lower and upper limits of quantification for SGC were 0.1 μg/ml and 8 μg/ml, respectively. A drug-sensitive assay measures concentrations of 'free' AGA and so is unable to detect these antibodies in the presence of circulating golimumab. AGA assay has a lower limit of detection of 2.5 μg/ml (assay range 2.5–80 μg/ml).

2.4 | Outcome measures and definitions

Clinical remission was defined as a PMS ≤2 with no individual subscore exceeding 1 point. We defined endoscopic healing as an MES of 0. Histologic remission was defined as a Geboes index ≤2.0. Biochemical remission was defined as FC <250 μg/g. Combined clinical-biochemical remission was defined as PMS ≤2 + FC <250 μg/g. Deep remission was defined as clinical remission (PMS ≤2) + endoscopic healing (MES = 0). Disease clearance was defined as clinical remission + endoscopic healing + histologic remission (Geboes ≤2.0). The short-term co-primary end points were the SGC thresholds that are associated with combined clinical-biochemical remission, deep remission and disease clearance during maintenance therapy.

The long-term outcome measures were the cumulative probabilities of golimumab dose escalation-free survival, golimumab discontinuation-free survival and colectomy-free survival between the day of SGC collection and the last follow-up. Golimumab dose escalation or discontinuation was decided by the attending gastroenterologist. This decision was independent of drug concentrations, as the SGC samples were analysed together at the end of the study and were not known to the investigators.

2.5 | Statistical analysis

Quantitative variables were summarised as median and interquartile range (IQR) or mean and standard deviation (SD). Qualitative variables were presented as absolute frequencies and proportions. Mean differences between continuous variables were calculated by using the *t*-Student test if normality criteria were met, or the Mann–Whitney U test if not. Categorical variables were compared using the chi-squared or Fisher's exact test. Linear-by-linear chi-squared test for trend was used to analyse SGC categorised into quartiles. Correlations were evaluated with Spearman or Pearson coefficients depending on the distribution of the variables. To evaluate variables associated with SGC, a linear regression model was performed in which statistically significant variables in univariate analysis were included in a backward stepwise multivariate analysis. Variables with $p > 0.20$ were removed from the final model. Results were expressed as standardised β-coefficient with 95% confidence intervals (CI). Receiver-operating characteristic (ROC) analyses were performed to identify SGC thresholds associated with outcomes. Optimal thresholds were determined using the Youden index, which maximises the sum of the specificity and sensitivity of the ROC curve.[22] In the long-term, golimumab dose escalation-free survival and golimumab discontinuation-free survival were estimated together (event-free survival) using survival analysis. The cumulative probability of the event-free survival associated with SGC thresholds was calculated by the Kaplan–Meier method. Results were considered statistically significant when $p < 0.05$. SPSS v. 22 (SPSS; IBM Corp.) was used for calculations.

2.6 | Ethical considerations

The study was performed according to the Declaration of Helsinki's ethical guidelines and was approved by the Clinical Research Ethics Committees of the participating centres (leading centre: Hospital Universitario Clínico San Carlos, Madrid, Spain; C.I. 18/396-O_SP, 17 August 2018). All enrolled patients provided written consent for their participation in the study. The study was registered with ClinicalTrials.gov Identifier: NCT03773445.

3 | RESULTS

3.1 | Patient characteristics

From March 2019 to October 2021, 52 consecutive patients receiving golimumab maintenance therapy were included in 10 IBD referral units throughout Spain. Demographic and clinical characteristics of patients and disease activity at the time of therapeutic drug monitoring are summarised in Table 1. All patients received induction with SC golimumab 200 mg at week 0 and 100 mg at week 2. At inclusion, 15 patients (28.8%) with body weight <80 kg were receiving maintenance with golimumab 50 mg every 4 weeks, and 37 patients (71.1%) were receiving 100 mg every 4 weeks. Among patients

receiving 100 mg every 4 weeks, 20 had a body weight ≥80 kg and were on standard maintenance dosing. The remaining 17 patients had a body weight <80 kg and had previously been dose escalated from 50 mg to 100 mg every 4 weeks. The median duration of golimumab exposure was 23 (IQR 15–32; range 5–76) months. All but two collected serum samples were golimumab trough concentrations, taken just before the scheduled SC golimumab administration. In two patients, samples were obtained 1 day before golimumab administration. There were no missing data, except for one patient without FC samples.

3.2 | Golimumab trough concentrations: Overall and according to demographics and golimumab dosing

The overall median SGC during maintenance was 1.79 μg/ml (IQR 0.87–2.79, range <0.1–5.93). Three patients (5.7%) had undetectable SGC (<0.1 μg/ml) together with positive AGA (12.2, 15.6 and 89.1 μg/ml, respectively). None of the patients with positive AGA and undetectable SGC achieved combined clinical-biochemical remission, endoscopic healing or histologic remission, although one of them was in clinical remission. In all three patients, golimumab was discontinued during follow-up, although the investigators were not aware of SGC or AGA status at the time.

Median (IQR) SGC for patients weighing <80 kg or ≥ 80 kg on standard dosing (50 mg or 100 mg every 4 weeks) were 1.61 (0.80–2.23) and 1.99 (0.93–2.72), respectively ($p = 0.859$). Patients with body weight < 80 kg who were dose escalated to 100 mg every 4 weeks had a median (IQR) SGC of 2.29 (0.75–3.26) ($p = 0.263$ and $p = 0.317$ vs. patients weighing <80 kg or ≥ 80 kg on standard dosing, respectively). Median SGC according to demographic characteristics, golimumab dosing and outcomes are shown in Table S1. Patients with BMI <24 had significantly higher SGC ($p = 0.022$).

TABLE 1 Demographic and clinical characteristics of patients at the time of therapeutic drug monitoring ($N = 52$)

Sex, female, *n* (%)	28 (53.8)
Age, years, mean (SD)	48 (13)
Body mass index, mean (SD)	24 (4)
Smoker, *n* (%)	
Current	1 (1.9)
Ex-smoker	24 (46.1)
Never smoker	27 (51.9)
Duration of disease, years, mean (SD)	12 (7)
Extent of disease, *n* (%)	
E1 (proctitis)	3 (5.7)
E2 (left-sided colitis)	15 (28.8)
E3 (extensive colitis)	34 (65.4)
Concomitant immunosuppressant, *n* (%)	18 (34.6)
Concomitant topical treatment, *n* (%)	17 (32.3)
Concomitant corticosteroids, *n* (%)	2 (3.8)
Golimumab maintenance dose, *n* (%)	
100 mg every 4 weeks	37 (71.1)
50 mg every 4 weeks	15 (28.8)
Dose escalation from 50 mg to 100 mg every 4 weeks, *n* (%)	19 (36.5)
Dose de-escalation from 100 mg to 50 mg every 4 weeks, *n* (%)	2/19 (10.5)
Time with golimumab, months, median (IQR)	23 (15–32)
Anti-TNF naïve, *n* (%)	37 (71.1)
Time with prior biologic, months, median (IQR)	18 (7–41)
Partial Mayo score, mean (range)	0.8 (0–5)
Mayo endoscopic subscore, median (IQR)	1 (0–2)
C-reactive protein, mg/dL, median (IQR)	0.29 (0.11–0.49)
Calprotectin, μg/mg, median (IQR)	234 (74–803)
Geboes index, median (IQR)	4 (2–5)

3.3 | Relationship between golimumab trough concentrations and outcomes

With a median of 23 (IQR 15–32) months of golimumab therapy, 46 patients (88%) were in clinical remission (PMS ≤2), and 26 patients (52%) had combined clinical-biochemical remission. Eighteen patients (35%) achieved endoscopic healing (MES 0), and all of them were in clinical remission. Therefore, the analysis of the results for endoscopic healing and deep remission was the same. Twenty-one patients (40%) had histologic remission, and 14 patients (27%) achieved disease clearance.

Median SGC during maintenance were significantly higher in patients achieving clinical remission ($p = 0.047$), combined clinical-biochemical remission ($p = 0.041$), endoscopic healing and deep remission ($p = 0.003$), histologic remission ($p = 0.02$) and disease clearance ($p = 0.009$), compared with those not meeting these criteria (Figure 1).

3.4 | Golimumab trough concentrations quartile analysis

There were no differences in combined clinical-biochemical remission rates according to SGC divided into quartiles ($p = 0.075$). The higher SGC quartiles were associated with statistically significantly higher rates of endoscopic healing ($p = 0.005$) and of histologic remission ($p = 0.006$). (Figure 2).

3.5 | Golimumab trough concentrations threshold associated with outcomes

ROC curve analysis and optimal SGC thresholds most closely associated with key outcomes are presented in Figure 3. ROC curve analysis identified an SGC threshold ≥0.85 μg/ml (area under the

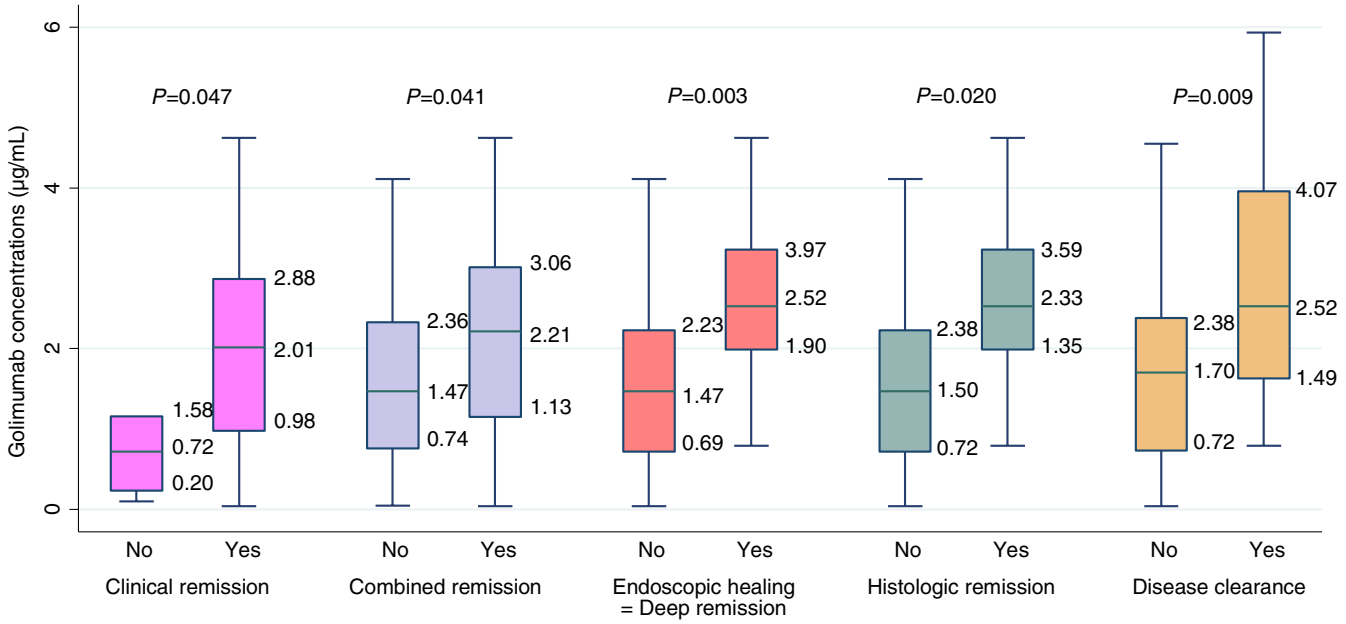
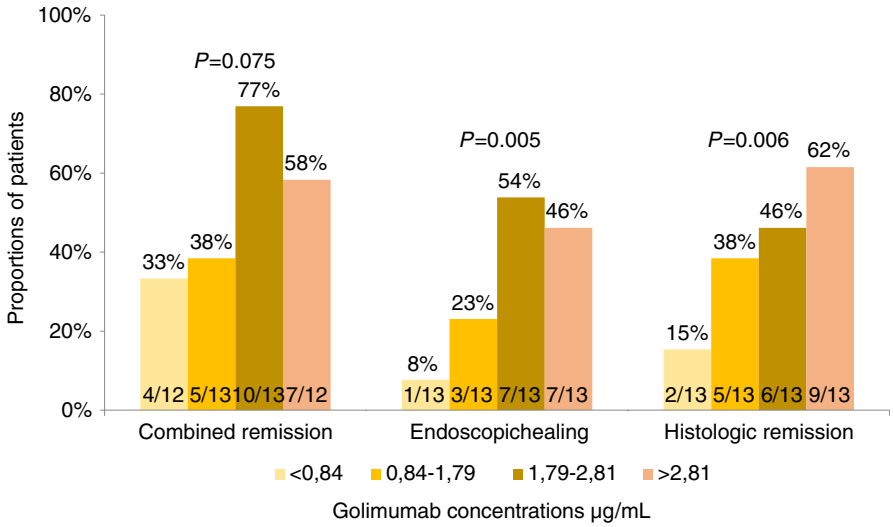


FIGURE 1 Median golimumab trough concentrations during maintenance: Differences between patients who achieved clinical remission, combined clinical-biochemical remission, endoscopic healing = deep remission, histologic remission and disease clearance, and those who did not

FIGURE 2 Proportions of patients achieving combined clinical-biochemical remission, endoscopic healing and histologic remission by serum golimumab trough concentration quartiles during maintenance



ROC curve [AUROC] 0.76, $p = 0.038$) to be significantly associated with clinical remission (sensitivity [SN] 80%, specificity [SP] 67%, positive predictive value [PPV] 95% and negative predictive value [NPV] 31%). An SGC threshold ≥1.90 µg/ml (AUROC 0.76, $p = 0.045$) was significantly associated with clinical-biochemical remission (SN 65%, SP 69%, PPV 68% and NPV 67%). (Figure 3A) An SGC threshold ≥2.29 µg/ml (AUROC 0.75, $p = 0.003$) was significantly associated with the achievement of endoscopic healing and deep remission (SN 67%, SP 79%, PPV 63% and NPV 82%). (Figure 3B) An SGC threshold of ≥1.79 µg/ml (AUROC 0.68, $p = 0.026$) was significantly associated with histologic remission (SN 67%, SP 61%, PPV 54% and NPV 73%). (Figure 3C) Finally, an SGC threshold ≥2.29 µg/ml (AUROC of 0.72, $p = 0.017$) was significantly associated with achieving disease clearance (SN 64%, SP 74%, PPV 47% and NPV 85%). (Figure 3D).

3.6 | Golimumab trough concentrations and Health-Related quality of life

Patients reported a notably high HRQoL for all five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) of the EQ-5D. The mean total EQ-5D score was 0.884 (SD 0.141), where 1.000 represents the best imaginable health. The mean EQ-5D VAS score was 79.9 (SD 17), where 100 represents the best imaginable health. There were no differences in EQ-5D score

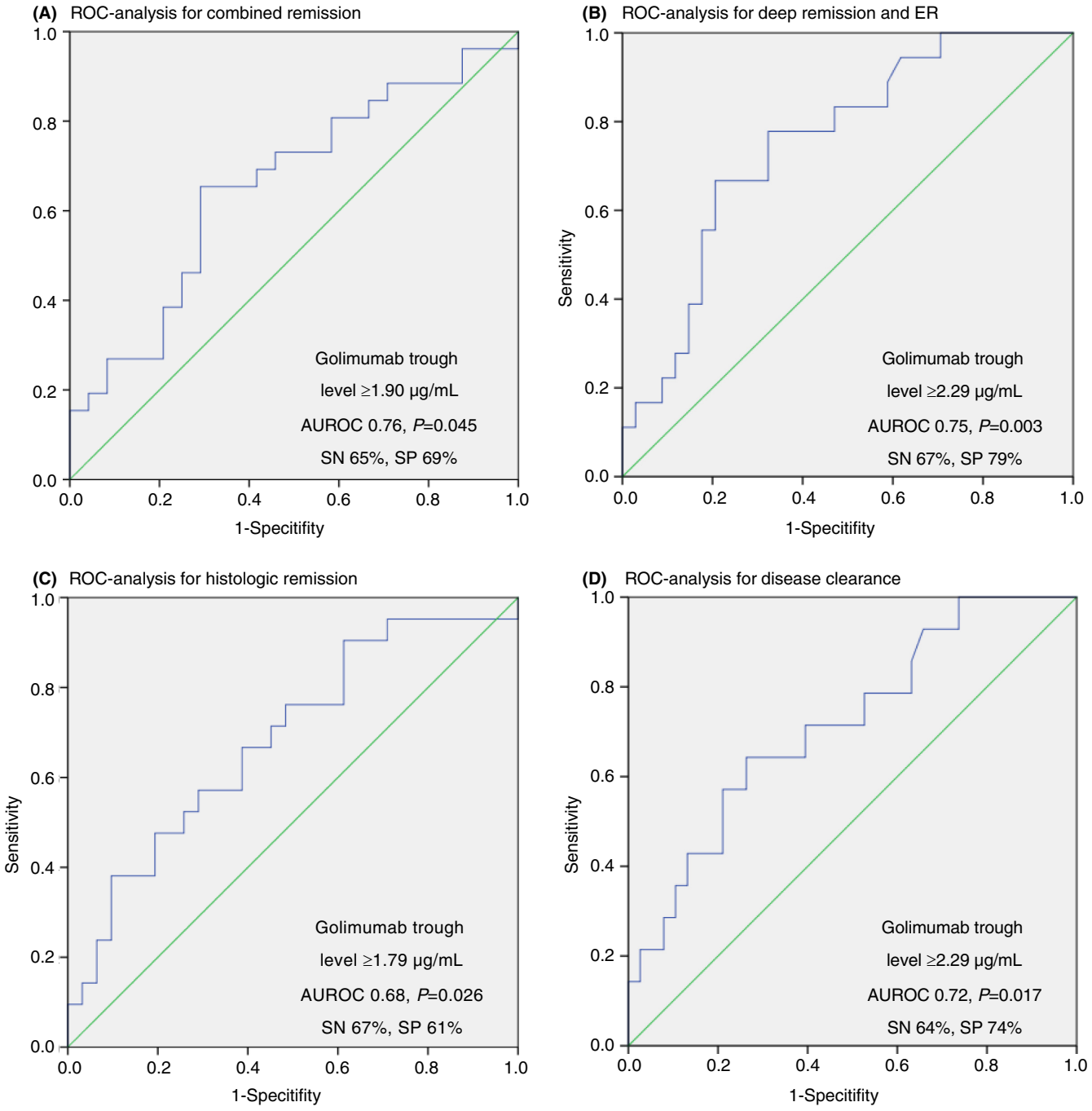


FIGURE 3 Receiver operating characteristic [ROC] analysis to determine the serum golimumab trough concentrations thresholds during maintenance most closely associated with key outcomes: (A) ROC analysis for combined remission, (B) ROC analysis for deep remission and endoscopic remission (ER), (C) ROC analysis for histologic remission, (D) ROC analysis for disease clearance. AUROC, area under the ROC curve; SN, sensitivity; SP, specificity

(p = 0.115) and EQ-5D VAS score (p = 0.107) according to SGC divided into quartiles. Likewise, there was no linear correlation between SGC and EQ-5D-5L score (r = 0.264, p = 0.080) or EQ-5D VAS score (r = 0.201, p = 0.176).

Similarly, patients reported high HRQoL in the disease-specific SIBDQ, with a mean score of 77.9 (SD 18.1), where 100 represents the best imaginable health. The higher SGC quartiles were associated with a statistically significantly higher SIBDQ score (p = 0.025) (Figure S2A). There was a significant correlation between SGC and SIBDQ score (r = −0.394, p = 0.006) (Figure S2B).

Mean EQ-5D score, mean EQ-5D VAS score and mean SIBDQ score in patients achieving the specified outcomes compared with those who did not are shown in Table S2.

3.7 | Factors associated with golimumab trough concentrations

In the univariate analysis (Table 2), BMI, concomitant corticosteroids and elevated CRP were associated with lower SGC, whilst male sex, concomitant immunosuppressant and receiving golimumab 100 mg every 4 weeks in patients with body weight < 80 kg were associated with higher SGC. Variables with $p < 0.20$ were included in the logistic model, and multivariate analysis concluded that BMI ($p = 0.021$) and CRP level ($p = 0.040$) were linearly associated with lower SGC. Conversely, concomitant immunosuppressant treatment was significantly associated with higher SGC ($p = 0.047$). (Table 2).

We found no significant correlation between SGC and PMS ($r = -0145$, $p = 0.536$). SGC were inversely correlated with MES ($r = -0{,}323$, $p = 0{,}019$), Geboes index ($r = -0{,}395$, $p = 0{,}004$) and CRP ($r = -0.345$, $p = 0.012$).

3.8 | Golimumab trough concentrations and faecal calprotectin

We found a negative correlation between faecal calprotectin and SGC, but the degree of correlation was low ($r = -0.284$, $p = 0.043$; perfect negative correlation $r = -1$), (Figure S3) Patients with calprotectin <250 μg/g could have SGC above or below the optimal thresholds most closely associated with the prespecified outcomes.

Faecal calprotectin levels were consistently higher in patients achieving the specified outcomes compared with those who did not (Table S3). Therefore, we were able to identify optimal calprotectin thresholds most closely associated with clinical remission, endoscopic healing, histologic remission and disease clearance (Table S4).

3.9 | Predictive value of golimumab trough concentrations on long-term outcomes

After a median follow-up of 28 months (IQR 13.2–34.1), 34 of 52 patients (65.4%, 95% CI 51.5–79.3) avoided golimumab dose escalation or discontinuation (Figure S4). In 18 patients (34.6%, 95% CI 20.7–48.5), golimumab was discontinued (14 patients) or the golimumab dose was escalated (five patients, one was subsequently discontinued). The reasons for golimumab discontinuation were loss of response in 13 patients and adverse event in 1 patient (injection site reaction with induration). No patient needed colectomy. The median time to escalation/discontinuation of golimumab was 9.2 months (IQR 1.0–20.8). At the last follow-up, 38 patients were still on golimumab maintenance (73.0%, 95% CI 60.1–86.1). After discontinuation of golimumab, 11 patients received another biologic (four vedolizumab, two infliximab, one adalimumab and one ustekinumab), three tofacitinib and four conventional treatments.

Median [IQR] SGC were significantly higher in patients who avoided golimumab dose escalation/discontinuation (2.24 [1.37–2.94] μg/ml) compared with those who did not (0.98 [0.52–2.04] μg/ml,

TABLE 2 Univariate and multivariate linear regression analyses of factors associated with serum golimumab trough concentrations during maintenance therapy. Variables with $p < 0.20$ (bold) in univariate analysis were included in the logistic model

	Univariate analysis		Multivariate analysis	
	Beta standardised coefficient (95% CI)	***p***	**Beta standardised coefficient (95% CI)**	***p***
Sex, male	**0.22 (0.06 to 0.50)**	**0.117**		
Age	0.04 (−0.24 to 0.32)	0.774		
Duration of disease	0.14 (−0.14 to 0.42)	0.330		
Current smoker	0.19 (−0.09 to 0.46)	0.186		
Body mass index	**−0.35 (−0.63 to −0.07)**	**0.016**	**−0.31 (−0.58 to −0.05)**	**0.021**
Extent of disease, E3 (extensive colitis)	0.11 (−0.17 to 0.39)	0.440		
Months with Golimumab	−0.02 (−0.30 to 0.27)	0.901		
GLM 100 mg/4 week	0.13 (−0.15 to 0.41)	0.361		
GLM 100 mg/4 week/ body weight <80 kg	**0.28 (0.00 to 0.55)**	**0.046**		
Prior immunosuppressant	−0.10 (−0.38 to 0.18)	0.476		
Anti-TNF-naïve	0.09 (−0.19 to 0.38)	0.504		
Time with prior biologic	−0.31 (−0.88 to 0.25)	0.256		
Concomitant immunosuppressant	**0.22 (−0.06 to 0.49)**	**0.122**	**0.27 (0.00 to 0.53)**	**0.047**
Concomitant topical salicylate	−0.16 (−0.44 to 0.12)	0.270		
Concomitant oral salicylate	−0.12 (−0.40 to 0.16)	0.409		
Concomitant steroids	**−0.22 (−0.50 to 0.06)**	**0.119**		
C-reactive protein (mg/dl)	**−0.30 (−0.57 to −0.03)**	**0.029**	**−0.28 (−0.54 to −0.01)**	**0.040**

Abbreviation: GLM, golimumab.

$p = 0.012$). An SGC threshold ≥1.56 μg/ml (AUROC 0.71, $p = 0.012$) was significantly associated with event-free survival (SN 74%, SP 67%, PPV 81% and NPV 57%). Survival curves showed that patients with SGC ≥1.56 μg/ml had an increased probability of avoiding golimumab escalation/discontinuation ($p = 0.005$). (Figure 4).

4 | DISCUSSION

In this multicentre, real-world prospectively conducted cross-sectional study, we demonstrated a positive association of serum golimumab trough concentrations during maintenance therapy with key outcomes, including endoscopic healing, in patients with UC. Notably, to our knowledge, this study is the first to report the association of SGC with more stringent treatment targets like histologic remission and disease clearance. Additionally, we were able to identify SGC thresholds most closely associated with outcomes, which may also help guide decision-making in patients with UC receiving golimumab maintenance therapy.

Composite end points that included FC have been used increasingly in clinical trials and in the real world as a potential surrogate marker and non-invasive tool to facilitate care in the clinical setting.[3] In our maintenance cohort, we found an exposure–response relationship of SGC with a composite end point that included the combination of clinical (PMS ≤2) and biochemical (FC <250 μg/g) remission. During maintenance golimumab, the optimal SGC threshold most closely associated with clinical-biochemical remission was 1.9 μg/ml. The GO-LEVEL study by Samaan et al with the same ELISA kit reported a higher median SGC during maintenance in patients in

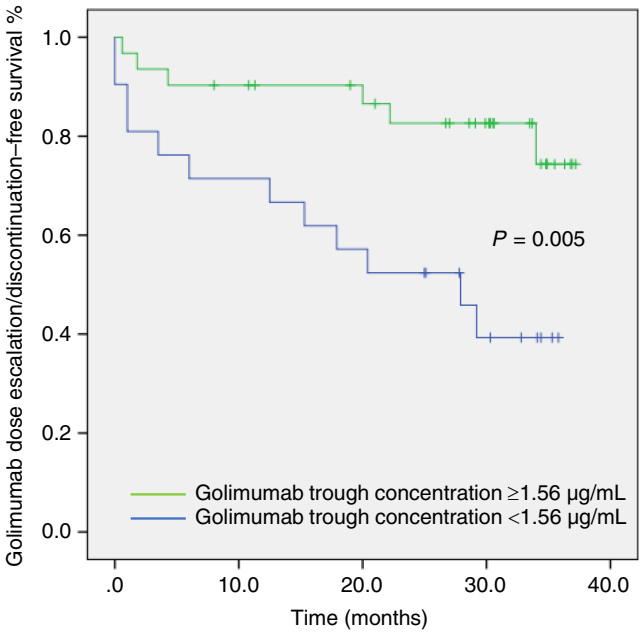


FIGURE 4 Cumulative probability of avoiding golimumab dose escalation and golimumab discontinuation: Differences in the survival curves between patients with golimumab trough concentration ≥1.56 μg/ml or <1.56 μg/ml (Kaplan–Meier method)

combined clinical-biochemical remission and a higher SGC threshold to achieve combined remission than our study.[16] A potential explanation of this difference is that, in our study, the proportions of patients naïve to anti-TNF and with concomitant treatment with immunosuppressants are lower than those of the GO-LEVEL study. Multivariate analysis showed that in our cohort, concomitant immunosuppressant treatment was significantly associated with higher SGC.

According to STRIDE evidence- and consensus-based recommendations for treat-to-target strategies in patients with UC, endoscopic healing was the preferred long-term treatment goal in UC.[3,23] Endoscopic healing is commonly defined as MES ≤1, but complete endoscopic remission (MES 0) is associated with superior disease outcomes.[3,24] Our study established an association between SGC and endoscopic healing defined as MES 0, with patients in higher SGC quartiles having higher rates of endoscopic healing. Several real-world studies reported the relationship between golimumab exposure during induction therapy and mucosal healing.[25–27] Conversely, the association of SGC with mucosal healing during maintenance has only been evaluated in the real world in a retrospective study that included 19 patients with UC or IBD-unclassified.[28] Although there was a trend towards a higher trough golimumab level in patients with endoscopic remission (defined as an MES of 0 or 1), this difference was not statistically significant, which is most likely due to the small sample size. No thresholds to achieve mucosal healing were identified in this cohort. For the first time in the real world, we were able to identify an SGC threshold of 2.29 μg/ml during maintenance, with 75% accuracy, for endoscopic healing.

With the arrival of biologics and small molecules for UC, it is time to explore possible ways to raise the bar in UC treatment and elucidate the potential role of histologic remission as the ultimate disease-modifying goal. Anti-TNF drugs, particularly infliximab, have been shown to be able to achieve and maintain histologic remission in a significant proportion of UC patients.[14,29] One-third of anti-TNF naïve patients with active moderate to severe UC achieve histologic remission with adalimumab maintenance therapy.[30] In contrast, clinical trial and real-world evidence regarding the ability of golimumab maintenance to achieve histologic remission is lacking. Using a standardised biopsy protocol and blinded central histopathology reading, we were able to demonstrate the ability of golimumab maintenance to induce histologic remission, measured as a Geboes index ≤2.0, in 40% of patients with UC. A novel finding of our study was establishing an association between SGC during maintenance and histologic healing and to identify an SGC threshold to achieve this outcome. Notably, quartile analysis evidenced that the rates of histologic remission did not reach a plateau with respect to increasing golimumab concentrations and continued to increase with higher drug concentrations. These data indicate that higher concentrations of golimumab may be required for certain patients to reach this more stringent end point of histologic cure.

Here, we report the positive association of SGC with disease clearance during maintenance with an optimal SGC threshold of 2.29 μg/ml to achieve this outcome. A finding of our study is that

progressively higher SGC may be required for certain patients to attain increasingly stringent therapeutic targets like endoscopic healing and disease clearance, as has been previously reported during maintenance therapy with infliximab.[14]

Higher body weight and higher inflammatory burden (e.g. higher CRP levels) are known to contribute to higher clearance of golimumab.[15] In our study, the multivariate analysis concluded that BMI and CRP level were linearly associated with lower SGC. These data may indicate that a subgroup of patients with higher BMI and higher inflammatory burden may potentially require higher doses of golimumab to achieve therapeutic goals. We found a highly significant association between FC levels and clinical outcomes. Although this finding was expected given that the correlation between FC and clinical and endoscopic remission has been reported by multiple studies, we consider these data to give consistency to the study. Given that the degree of correlation between FC and SGC was low, FC cannot substitute for SGC in our study.

An ultimate target of long-term treatment in UC should be the restoration of the patient's quality of life regardless of other objective markers of inflammation. A prior real-world study reported sustained improvements in HRQoL after 54 weeks of treatment with golimumab.[31] However, the association between SGC and HRQoL in UC patients has not been previously evaluated. Here, we report that higher SGC quartiles during maintenance were associated with statistically significantly better HRQoL evaluated with the SIBDQ.

The main limitation of the study is the lack of longitudinal TDM of SGC, which would be needed to establish an association between therapeutic outcomes and golimumab concentration, and not causality. It remains unclear if high golimumab concentrations are necessary to induce endoscopic or histologic remission, or if these outcomes were associated with high drug concentrations because of reduced drug clearance and faecal loss. Furthermore, the lack of prospective TDM prevents us from knowing the prognostic impact of the SGC at a given point in time. However, the study did assess long-term clinical outcomes, with two-thirds of patients avoiding golimumab dose escalation or discontinuation during maintenance, in line with previous real-world studies.[32,33] Here, we reported for the first time in a real-world setting the positive association of SGC at a time point with golimumab dose escalation-free or discontinuation-free survival during follow-up, with an optimal SGC threshold of 1.56 μg/ml and 71% accuracy, to achieve this outcome. Therefore, we believe that knowledge of SGC, together with clinical, endoscopic and histologic data, could help in making important therapeutic decisions in patients on golimumab maintenance. Since investigators decided golimumab dose escalation or discontinuation unaware of SGC, this study does not resolve the question about whether patients identified with low SGC can attain, regain or maintain efficacy if their golimumab exposure was to be increased. To address this question, a prospective study is required in which patients with low SGC undergo dose optimisation with the aim of reaching the identified thresholds and which also investigates the prognostic impact of the intervention on outcomes.

Another limitation of our study is the use of a drug-sensitive antidrug antibody assay that measures serum concentrations of 'free' or excess AGA and is not able to detect antibodies in the presence of the drug. Immunogenicity rates were very low, with three patients (5.7%) having positive AGA together with undetectable SGC (<0.1 μg/ml). Our study has several strengths. The prospective design allowed us to obtain, in all but two patients, the trough concentrations of golimumab taken just before scheduled subcutaneous administration and to minimise missing data. Endoscopy was performed on each patient at a maximum interval of 2 weeks with the extraction of levels. To avoid bias in the histologic analysis, samples were collected using a standardised biopsy protocol, pathologists were blinded for symptomatic and endoscopic activity and for golimumab levels and we used the well-validated Geboes index.[21]

In conclusion, we found in UC patients a relationship between golimumab trough concentrations during maintenance and favourable treatment outcomes including endoscopic healing, histologic remission and long-term persistence on golimumab. In addition, golimumab concentration thresholds most closely associated with key outcomes were identified, with higher concentrations needed to achieve increasingly stringent therapeutic targets. The identified SGC targets can provide a reliable starting point for future study designs to prospectively evaluate the utility of TDM and to confirm the usefulness of these SGC thresholds in the management of patients with UC.

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AUTHORSHIP

Guarantor of the article: Carlos Taxonera.

Author contributions: C.T. designed and conducted the research study. MJ.F. and C.DA. performed the central histologic reading. DO designed the database and performed the statistical analysis of the study. C.T., M.C., B.C., F.B., P.LS., M.I., F.M., M.BW., I.V., S.O., A.A., and C.A. selected and included the patients and were responsible for the acquisition of data and samples. All authors read and approved the final version of the manuscript.

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REFERENCES

1. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:85–95.
2. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:96–109.
3. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD: determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2021;160:1570–83.
4. Zenlea T, Yee EU, Rosenberg L, Boyle M, Nanda KS, Wolf JL, et al. Histology grade is independently associated with relapse risk in patients with ulcerative colitis in clinical remission: a prospective study. Am J Gastroenterol. 2016;111:685–90.
5. Bryant RV, Burger DC, Delo J, Walsh AJ, Thomas S, von Herbay A, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut. 2016;65:408–14.
6. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126:451–9.
7. Danese S, Roda G, Peyrin-Biroulet L. Evolving therapeutic goals in ulcerative colitis: towards disease clearance. Nat Rev Gastroenterol Hepatol. 2020;17(1):1–2.
8. Steenholdt C, Brynskov J, Thomsen OØ, Munck LK, Fallingborg J, Christensen LA, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. 2014;63:919–27.
9. Velayos FS, Kahn JG, Sandborn WJ, Feagan BG. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. Clin Gastroenterol Hepatol. 2013;11:654–66.
10. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut. 2010;59:49–54.
11. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148:1320–9.
12. Adedokun OJ, Sandborn WJ, Feagan BG, Rutgeerts P, Xu Z, Marano CW, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology. 2014;147:1296–307.
13. Vande Casteele N, Khanna R, Levesque BG, Stitt L, Zou GY, Singh S, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut. 2015;64:1539–45.
14. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Infliximab trough concentrations during maintenance therapy are associated with endoscopic and histologic healing in ulcerative colitis. Aliment Pharmacol Ther. 2018;47:478–84.
15. Adedokun OJ, Xu Z, Marano CW, Strauss R, Zhang H, Johanns J, et al. Pharmacokinetics and exposure-response relationship of Golimumab in patients with moderately-to-severely active ulcerative colitis: results from phase 2/3 PURSUIT induction and maintenance studies. J Crohns Colitis. 2017;11:35–46.
16. Samaan MA, Cunningham G, Tamilarasan AG, Beltran L, Pavlidis P, Ray S, et al. Therapeutic thresholds for golimumab serum concentrations during induction and maintenance therapy in ulcerative colitis: results from the GO-LEVEL study. Aliment Pharmacol Ther. 2020;52(2):292–302.
17. von Elm E, Altman DG, Egger M, STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
18. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199–208.
19. Irvine EJ, Zhou Q, Thompson AK. The short inflammatory bowel disease questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. Am J Gastroenterol. 1996;91:1571–8.
20. López-Vivancos J, Casellas F, Badia X, Vilaseca J, Malagelada JR. Validation of the Spanish version of the inflammatory bowel disease questionnaire on ulcerative colitis and Crohn's disease. Digestion. 1999;60:274–80.
21. Geboes K, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000;47:404–9.
22. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3:32–5.
23. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110:1324–38.
24. Barreiro-de Acosta M, Vallejo N, de la Iglesia D, Uribarri L, Bastón I, Ferreiro-Iglesias R, et al. Evaluation of the risk of relapse in ulcerative colitis according to the degree of mucosal healing (Mayo 0 vs 1): a longitudinal cohort study. J Crohns Colitis. 2016;10:13–9.

25. Detrez I, Dreesen E, Van Stappen T, de Vries A, Brouwers E, Van Assche G, et al. Variability in Golimumab exposure: a 'Real-Life' observational study in active ulcerative colitis. J Crohns Colitis. 2016;10:575–81.
26. Dreesen E, Kantasiripitak W, Detrez I, Stefanović S, Vermeire S, Ferrante M, et al. A population pharmacokinetic and exposure-response model of Golimumab for targeting endoscopic remission in patients with ulcerative colitis. Inflamm Bowel Dis. 2020;26:570–80.
27. Magro F, Lopes S, Silva M, Coelho R, Portela F, Branquinho D, et al. Low Golimumab trough levels at week 6 are associated with poor clinical, endoscopic and histological outcomes in ulcerative colitis patients: pharmacokinetic and Pharmacodynamic sub-analysis of the evolution study. J Crohns Colitis. 2019;13:1387–93.
28. Boland K, Greener T, Kabakchiev B, Stempak J, Tessolini J, Li R, et al. Identification of target golimumab levels in maintenance therapy of Crohn's disease and ulcerative colitis associated with mucosal healing. Inflamm Bowel Dis. 2019;26:766–73.
29. Magro F, Lopes SI, Lopes J, Portela F, Cotter J, Lopes S, et al. Histological outcomes and predictive value of Faecal markers in moderately to severely active ulcerative colitis patients receiving infliximab. J Crohns Colitis. 2016;10:1407–16.
30. Fernández-Blanco JI, Fernández-Díaz G, Cara C, Vera MI, Olivares D, Taxonera C. Adalimumab for induction of histological remission in moderately to severely active ulcerative colitis. Dig Dis Sci. 2018;63:731–7.
31. Probert CS, Sebastian S, Gaya DR, Hamlin PJ, Gillespie G, Rose A, et al. Golimumab induction and maintenance for moderate to severe ulcerative colitis: results from GO-COLITIS (Golimumab: a phase 4, UK, open label, single arm study on its utilization and impact in ulcerative colitis). BMJ Open Gastroenterol. 2018;5(1):e000212. https://doi.org/10.1136/bmjgast-2018-000212
32. Taxonera C, Rodríguez C, Bertoletti F, Menchén L, Arribas J, Sierra M, et al. Clinical outcomes of golimumab as first, second or third anti-TNF agent in patients with moderate-to-severe ulcerative colitis. Inflamm Bowel Dis. 2017;23:1394–402.
33. Taxonera C, Iborra M, Bosca-Watts MM, Rubio S, Nantes Ó, Higuera R, et al. Early dose optimization of golimumab induces late response and long-term clinical benefit in moderately to severely active ulcerative colitis. Curr Med Res Opin. 2019;35:1297–304.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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