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Alimentary Tract

Golimumab improves health-related quality of life of patients with moderate-to-severe ulcerative colitis: Results of the go-care study

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ABSTRACT

Background: In recent years, improvement of Health-Related Quality of Life (HRQoL) in Ulcerative colitis (UC) has become a relevant measure for treatment efficacy.
Methods: We report results from a multicenter prospective study in Italy investigating HRQoL in adult patients with UC treated with golimumab (GLM). Patients who had shown clinical response after a 6-week induction phase (w0), were followed for an additional 48 weeks (w48) (total 54-week treatment).
Results: Of the 159 patients enrolled 90 completed the study. Compared to values at the beginning of treatment ($n = 137$), significant improvements were observed for mean total Inflammatory Bowel Disease Questionnaire (IBDQ) scores at w0 (168.5) and w48 (181.7). Patients with baseline PMS above the median tended to have greater improvements in IBDQ at w0 (OR 2.037, $p = 0.033$) and w48 (OR 3.292, $p = 0.027$). Compared to beginning of GLM treatment, the mean Full Mayo Score (FMS) decreased by 5.9 points at w48, while mean Partial Mayo Score (PMS) decreased by 3.9 points at w0 and by 4.9 points at w48.

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Conclusions: GLM improved HRQoL, disease activity and inflammatory biomarkers in UC patients with moderate-to-severely active disease. The greater the burden of disease activity at baseline, the greater the improvement of HRQoL after 24 and 48 weeks of treatment.

1. Introduction

Ulcerative colitis (UC) is a chronic disorder belonging to inflammatory bowel disease (IBD), resulting from a complex interaction between genetics, environmental factors, immune response and gut microbiota [1]. UC is characterized intestinal symptoms (flare are diarrhea, bloody stools abdominal pain, tenesmus and urgency), with typical relapsing-remitting course and which in most severe cases (fever and weight loss) require therapies that may expose patients to infectious and neoplastic risks [1–3]. Also, the course of UC may be further complicated by the occurrence of extraintestinal manifestations [4], colorectal cancer [5] and, in approximately 15% of cases, by the need for colectomy with ileal pouch anal-anastomosis (IPAA) [6].

Disease symptoms-particularly bowel frequency and urgency of defecation-exert a strong negative impact on the lives of patients with UC, interfering with the individual's social life, work productivity, sexuality and other domains. Indeed in literature, symptoms of disease activity are consistently associated to worse health-related quality of life (HRQoL) compared to age and sex-matched populations and to patients affected by other severe chronic disease [7–12]. In particular, stress, anxiety, depression, and fatigue appear to cover a relevant toll on overall HRQoL [13–17]. Accordingly, an increasing number of studies are including HRQoL assessments as efficacy outcomes alongside more traditional measures of disease activity [18–21].

Golimumab, a subcutaneously administered fully human antibody towards tumor necrosis factor alpha (TNFalpha), has been shown to induce and maintain clinical remission in patients with moderate-to-severe active UC disease [22–24]. In the last years, several studies have also demonstrated the effectiveness of golimumab in clinical practice, including in patients previously treated with other anti-TNFs [25–28]. A Cochrane metanalysis, comparing the impact of several biologic therapies on the HRQoL in UC, was unable to provide conclusions for golimumab due to the paucity of available data [21]. Since then, additional real-world studies have assessed the impact of golimumab on HRQoL of UC patients [25,29–32].

The present study ("GO-CARE") aimed to assess the impact of golimumab on HRQoL and disease activity in a real-life setting of patients with active UC who had responded to a 6-week induction regimen.

2. Methods

2.1. Ethical considerations

This is a multicenter observational prospective study conducted from July 2015 to April 2021 across 34 IBD referral centers in Italy. The study protocol and its amended version were approved by Agenzia Italiana del Farmaco (AIFA) and by the Independent Ethics Committee of each center. The study was carried out in agreement with the Declaration of Helsinki. Collection, documentation, and reporting activities were in compliance with the protocol and accepted standards of Good Pharmacoepidemiology Practice.

All patients provided written informed consent prior to their participation.

2.2. Patients

The study enrolled adult (18–70 years old) patients diagnosed with UC, either naiïve or previously-exposed to anti-TNFs, who achieved clinical response at the end of a 6-weeks induction phase with golimumab. Golimumab was started due to moderate-to-severely active UC, defined as Full Mayo Score (FMS) [33] $\geq$6 (with endoscopic score $\geq$2). Exclusion criteria included a primary non-response to golimumab, ongoing treatment with other anti-TNFs or biologic agents for UC or other disease, and any contraindications to golimumab therapy. For each patient, demographic and clinical features, including disease history, comorbidities, and ongoing/previous treatments (including CCS, 6MP, AZA and anti-TNFα), concurrent therapy (CCS, 6MP, AZA), were collected by means of a dedicated eCRF.

2.3. Objectives

The primary objective was to evaluate predictors of IBDQ score improvement (greater or less than 16 points) achieved at w0 (six weeks after the start of golimumab induction therapy) and w48 (54 $\pm$ 3 weeks after the start of induction therapy) compared to the start of induction therapy.

Secondary objectives included the evaluation of the mean change in IBDQ scores; IBDQ score $\geq$170 points; the mean variation in FMS and PMS; the percentage of patients showing clinical response and clinical remission; the percentage of patients showing mucosal healing; the percentage of patients discontinuing treatment.

2.4. Drug administration

Treatment with golimumab includes an induction phase consisting of an initial 200 mg injection followed by an injection of 100 mg after 2 weeks. The maintenance phase continues with injections every four weeks. Initially, the maintenance dose was 50 or 100 mg according to body weight $\langle$ or $\rangle$ 80 kg, respectively; in July 2018, the European Medicine Agency (EMA) also allowed dose escalation to 100 mg for patients weighing less than 80 kg who had an inadequate response to induction therapy at week 6. The study protocol was amended to incorporate this new dosing option.

2.5. Inflammatory bowel disease questionnaire (IBDQ)

IBDQ is a 32-item questionnaire, divided into 4 health domains: bowel symptoms (10 questions), systemic symptoms (5 questions), emotional function (12 questions), social function (5 questions) [34]. For each question, there are graded responses on a 7-point Likert scale, ranging from 1 (representing the "worst" aspect) to 7 (representing the "best" aspect). The total IBDQ score ranges from 32 to 224, with higher scores reflecting better well-being. Mean score increases of 16 points have been linked to a clinically meaningful change while scores $\geq$170 points have been linked to remission [30,34]. The Italian translation of IBDQ used in the present study has been already validated [35].

2.6. Study timeline

The baseline index visit (w0) for the patients who participated in the study was performed at the end of the 6-weeks induction phase with golimumab.

Enrolled patients underwent clinical examination with assessment of Partial Mayo Score (PMS) [36] every 8 ± 3 weeks: w0, w8, w16, w24, w32, w40, w48. Part of this study was conducted during the COVID-19 pandemic; during the lockdown period, most of the monitoring visits were conducted remotely.

Blood chemistry [including Full Blood Count, C-Reactive Protein (CRP), Erythrocytes Sedimentation Rate (ESR), ferritin, serum protein electrophoresis, blood urea nitrate (BUN), creatinine and transaminases] was performed at the start of golimumab therapy and at w0, w24 and w48.

IBDQ was administered at the beginning of golimumab therapy as well as at w0, at w24 and w48.

Colonoscopy was performed within 3 months of starting golimumab therapy and at w48.

2.7. Definitions

The modified Full Mayo Score (FMS) was calculated considering stool frequency rectal bleeding, and endoscopic findings.

Clinical response in terms of PMS was defined as the decrease of ≥2 points or at least 30% in the PMS, and a decrease ≥1 point in rectal bleeding evaluated every 8 weeks from the start of GLM induction therapy. Whereas in terms of FMS it was defined as the decrease from baseline of FMS of at least 3 points or at least 30%, accompanied by either a rectal bleeding subscore of 0 or 1 or a decrease of at least 1 point from the start of GLM induction therapy (evaluated at w48).

Clinical remission in terms of PMS was defined as a PMS ≤2, with no individual subscore exceeding 1, as evaluated every 8 weeks, from w0 to w48; clinical remission in terms of FMS, was defined as a FMS ≤2, with no individual subscore exceeding 1, as evaluated every 8 weeks, from w0 to w48.

Finally, Mucosal healing was defined as endoscopic subscore of 0 or 1.

2.8. Statistical analysis

A descriptive analysis of demographic and clinical features was performed by tabulating absolute and relative frequencies for categorical variables and mean and standard deviation for continuous variables.

Univariate and multivariate logistic regression models were performed considering the dichotomous variable IBDQ score improvement at w0 and w48 as a dependent variable and exploring potential predictors as independent variables. Odds ratios (OR) were calculated together with the corresponding 95% Confidence Interval (CI) computed using Wald test statistic. Simple and multiple logistic regression analysis considered the following predictors of IBDQ score: age (<40 years vs ≥40 years); sex (Male/Female); BMI (<25 kg/m^2 vs ≥25 kg/m^2); PMS (<median value vs ≥median value); FMS (<median value vs ≥median value); endoscopic subscore (<median value vs ≥median value); previous therapies, at least one among oral 5-ASA, oral steroids, thiopurines (Yes/No); previous therapy with anti-TNFs (Yes/No); concomitant therapy, at least one among oral 5-ASA, oral steroids, thiopurines (Yes/No); concomitant topical therapy (categorized as Yes/No); steroid-dependence (Yes/No); ESR (<30 mm/h vs ≥30 mm/h); CRP (within range vs out of range); disease duration (<median value vs ≥median value); disease extension (proctitis, left-sided colitis, pancolitis) and smoking status (never vs smoker or former smoker).

Predictors were considered at baseline values (beginning of Golimumab therapy). For the primary objective, only statistically significant results were reported.

For the main secondary objectives, the mean change in IBDQ from the start of golimumab therapy was evaluated at w0, w24 and w48, and the corresponding Student's *t*-test *p*-values (paired data) for testing the improvement of at least 16 points were reported.

In addition, the proportion of patients with IBDQ greater than 170 points was evaluated at w0, w24 and w48, and the corresponding Student's *t*-test *p*-values (paired data) with respect to the start of golimumab therapy were reported.

Moreover, for each specific IBDQ domain the mean change from the beginning of therapy with GLM and the corresponding Student's *t*-test *p*-values (paired data) for testing the improvement of at least 1 point at w0, w24 and 48 were reported.

Other secondary objectives included the mean changes in PMS and FMS measured at w0, w24 and w48 relative to the start of GLM therapy. For the median variation at w0, w24 and w48 the corresponding p-values, obtained through the Wilcoxon Signed Rank Test, were also reported. Also the values of the modified Mayo Score were reported.

Measurements for each time point considered only the number of patients that were still in the study at that specific time point, in agreement with the study Protocol. Missing data were excluded from the analyses.

Statistical analyses were performed using SPSS statistical software, version 23.0.

3. Results

3.1. Patient population

The study had initially enrolled 154 patients across the participating centers, and then an additional 22 patients following the amendment of the protocol. Of these total 176 patients, 17 did not meet study eligibility criteria and were excluded from the study, leaving a total of 159 patients.

Among the 159 eligible patients who were included for descriptive demographic analyses and search for predictors for IBDQ improvement, 90 completed the study (Fig. 1).

3.2. Golimumab discontinuation

Sixty-nine of 159 (43.4%) enrolled patients discontinued Golimumab (GLM) treatment after a mean (±SD) of 27.8 weeks (±13.8). The most frequent reasons for discontinuation were loss of efficacy (43/159 patients, 27%) and loss to follow-up (13/159 patients, 8.2%).

Measurement at each time point considered only the number of patients who were still in the study at that specific time.

3.3. Baseline values

Demographic and clinical features, at the start of Golimumab therapy, of eligible patients are shown in Table 1.

Participants had a mean age of 43.4 years and mean disease duration of 9.7 years. Mean baseline FMS was 7.9 and mean baseline PMS was 5.7. The majority (83.6%) of patients had moderate disease. Most patient (88.7%) had been receiving corticosteroid therapy, while substantially fewer (20.8%) remained on concomitant therapy. Less than a quarter (23.3%) the patients had received previous anti-TNF treatment.

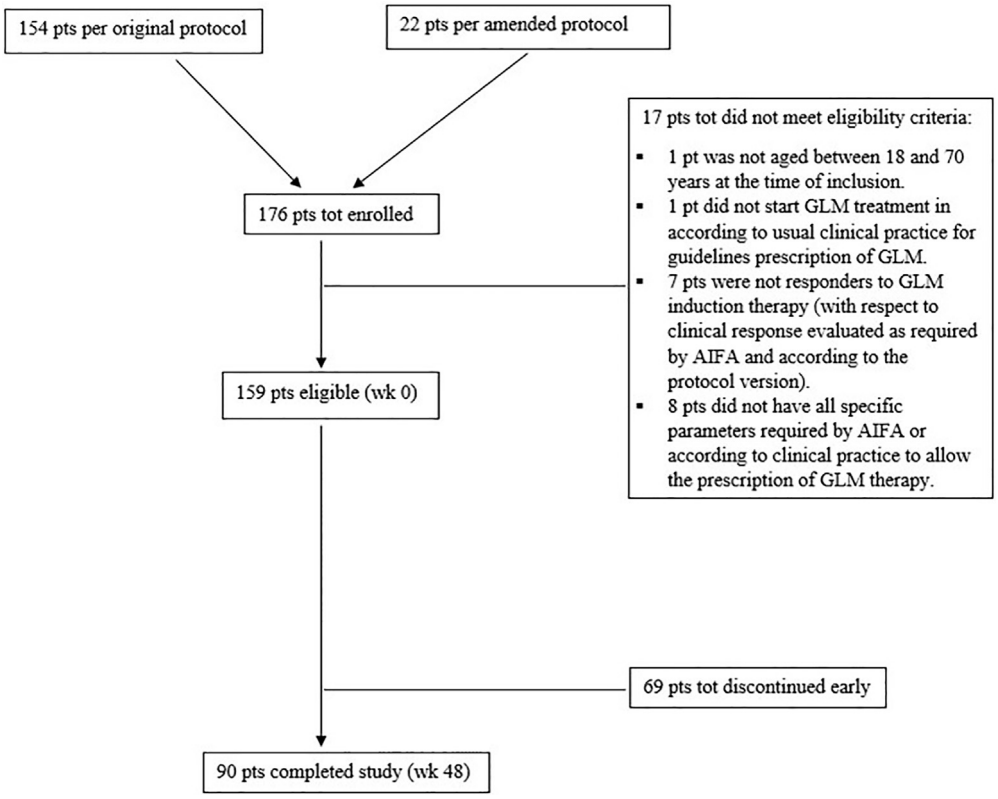

Fig. 1. Study flowchart. Pts = Patients. Tot = Total. GLM = Golimumab.

Table 1
Characteristics of enrolled patients.

N = 159	
Age (years, mean±SD)	43.4 ± 13.1
Gender (n,%)	
Male	101 (63.5%)
Female	58 (36.5%)
Weight (kg, mean±SD)	70.7 ± 14.5
BMI (kg/m^2 mean±SD)	24.5 ± 4.5
ESR (mm/h, mean±SD)	25.3 ± 19.9
CRP (mg/L, mean±SD)	11.8 ± 42.2
Disease duration (years, mean±SD)	9.7 ± 8.4
PMS (mean±SD)	5.7 ± 1.4
FMS (mean±SD)	7.9 ± 1.5
Disease activity (*n*,%)	
Moderate	133 (83.6%)
Severe	26 (16.4%)
Endoscopic subscore (mean±SD)	2.2 ± 0.5
Disease extension (*n*,%)	
Proctitis	13 (8.2%)
Left-sided colitis	74 (46.5%)
Pancolitis	72 (45.3%)
Previous therapy	
Steroids (*n*,%)	141 (88.7%)
Thiopurines (*n*,%)	64 (40.3%)
Anti-TNFs (*n*,%)	37 (23.3%)
Concomitant therapy	
Steroids (*n*,%)	33 (20.8%)
Thiopurines (*n*,%)	17 (10.7%)
IBDQ (mean±SD)	137.0 ± 41.0
Smoking status (*n*,%)	
Current/former smoker	64 (40.3%)
Never smoker	95 (59.7%)

CRP: C-Reactive Protein.
ESR: Erythrocyte Sedimentation Rate.
FMS: Full Mayo Score.
PMS: Partial Mayo Score.
TNF: Tumor Necrosis Factor.

3.4. Disease activity indices

Compared to the start of the GLM therapy, a mean (±SD) decrease of 5.9 points (±2.9) was observed for FMS at w48 (Fig. 2). Whereas the modified Mayo Score decreased from a mean (±SD) of 5.9 (±1.3) points, at the start of GLM therapy, to a mean of 1.6 (±2) points at w48.

A mean (± SD) decrease of 3.9 points (±1.6), 4.5 points (±2) and 4.9 points (±1.9) was observed for PMS at w0, w24 and w48 respectively, compared to the start of the GLM therapy (Fig. 2).

Given the characteristics of PMS and FMS a non-normal distribution, the comparison at each timepoint was performed with respect to the median values.

The median PMS was 2.00 at w0, and 0.00 at w24, and 0. w48. The differences between each of these median PMS values at w0, at w24 and w48 and their baseline value at the start of GLM therapy (equal to 6.00) and resulted statistically significant (p-value < 0.001 for all tests).

The median FMS at w48 was equal to 1.00; from the comparison between this median and the one at the start of GLM therapy, equal to 8.00, the change at w48 resulted statistically significant (p-value < 0.001 for all tests).

Among enrolled patients, clinical response and clinical remission as expressed in terms of PMS was reached by 100/117 patients (85.5%) and 95/117 patients (81.2%), and at w48 was reached by 81/90 (90%) and 80/90 (88.9%). At w48, 49/57 (86%) patients reached clinical response and 39/57 (68.4%) patients reached clinical remission according to FMS.

Of patients with available endoscopy, 42/56 (75%) achieved mucosal healing at w48.

All measurements considered only patients still in the study at the time of the measurement, as foreseen by the protocol.

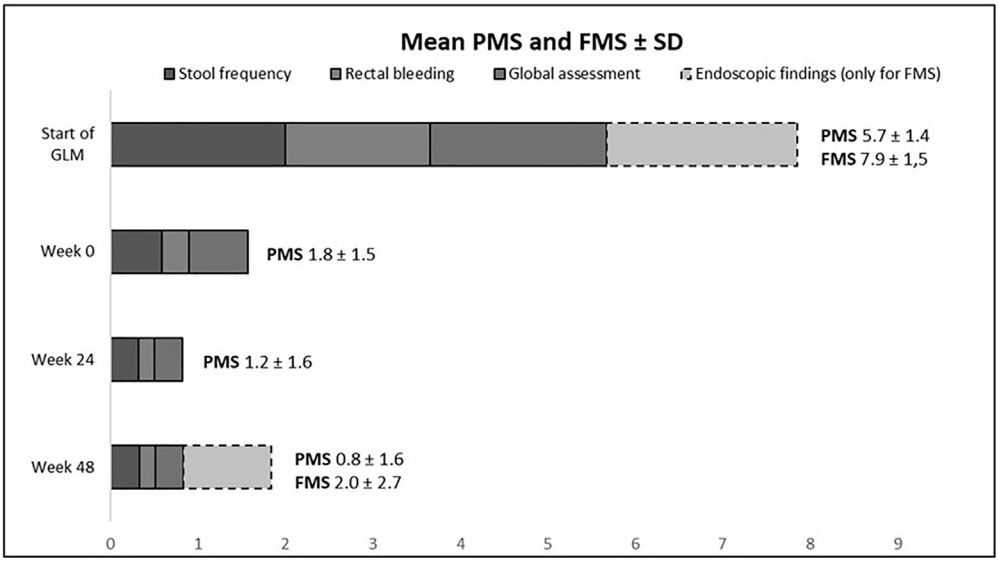

Fig. 2. Partial and Full Mayo Score. PMS = Partial Mayo Score. FMS = Full Mayo Score. SD = Standard Deviation. GLM = Golimumab.

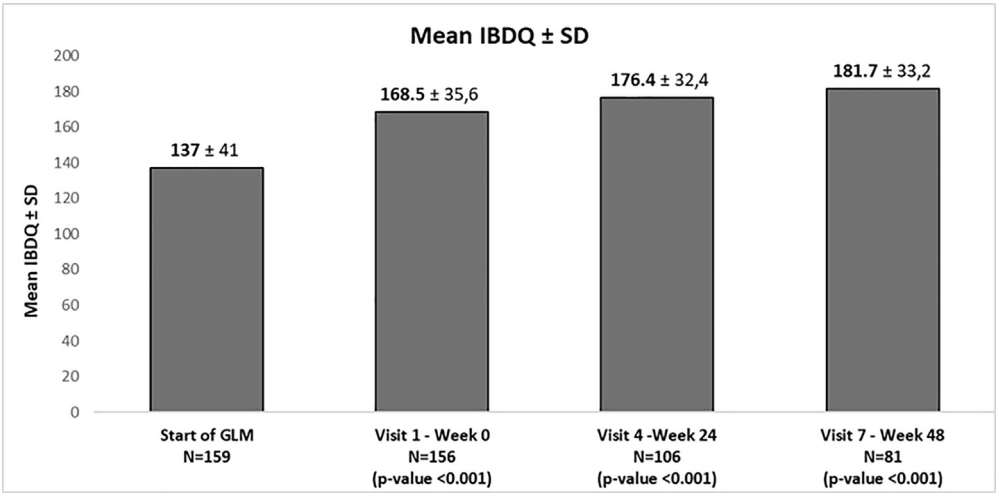

Fig. 3. Changes in mean IBDQ values (±SD). IBDQ = Inflammatory Bowel Disease Questionnaire. SD = Standard Deviation.

3.5. IBDQ improvement

Gradual improvements in IBDQ score among patients who had a clinical response to GLM were observed over time relative to the start of GLM therapy. At w0 (end of induction), 61.5% of patients within the study at that time had an IBDQ score increase of ≥16 points, with a mean increase of 31.4 points (p-value < 0.001). At w24, 70.8% of patients had an IBDQ score increase of ≥16 points, with a mean increase of 31.5 points (p-value < 0.001). At w48, 75.3% of patients had an IBDQ score increase of ≥16 points, with a mean increase of 46.4 (p-value < 0.001) (Fig. 3 and Supplementary Table S-1).

Stratification of patients based on prior anti-TNFs therapy (naïve vs non-naïve) suggests a trend of increasing IBDQ scores over time for both groups, with a slightly lower proportion of patients with improved IBDQ total scores among anti-TNF experienced patients compared to anti-TNF naïve patients at all timepoints (Table 2).

Patients with IBDQ score greater than 170 points were 54.5% at w0, 66% at w24 and 67.9% at w48; all percentages were significantly higher compared to the score at the start of GLM therapy (p-value < 0.001).

Upon analysis of the four IBDQ domains, a significant mean increase (±SD) was observed for all the scores, with the greatest improvements observed in the emotional and bowel domains, 16.4 points (±15.2) (with a mean percentage variation of 49.2%) and 13.7 points (±13) (with a mean percentage variation of 42.8%), respectively (Fig. 4). The mean increase of the score of all the domains was statistically significant at w0, w24 and w48 compared to GLM starting therapy (p-value < 0.001 for each time point).

3.6. Predictors of IBDQ improvement

Among the several parameters evaluated as potential predictors of IBDQ improvement only PMS and FMS showed an independent association.

In particular, patients with PMS above the median value, at the start of GLM therapy, had a 2-fold higher tendency to improve the IBDQ at w0 (OR = 2.037; p-value = 0.033), a 5-fold higher tendency to improve the IBDQ at w24 (OR = 5.194; p-value < 0.001) and a 3-fold higher tendency of attaining IBDQ improvement at w48 (OR = 3.292; p-value = 0.027) compared to those with lower baseline PMS (Supplementary Table S-2).

Table 2
IBDQ improvement by prior anti-TNF status.

		IBDQ improved					
		w0		W24		w48	
		N	Improved, n (%)	N	Improved, n (%)	N	Improved, n (%)
Prev. anti-TNFs	Naïve	119	76 (63.9)	80	60 (75)	67	52 (77.6)
	Not Naïve	37	20 (54.1)	26	15 (57.7)	14	9 (64.3)

IBDQ = Inflammatory Bowel Disease Questionnaire.
Prev. anti-TNFs = Previous therapy with anti-TNFs.

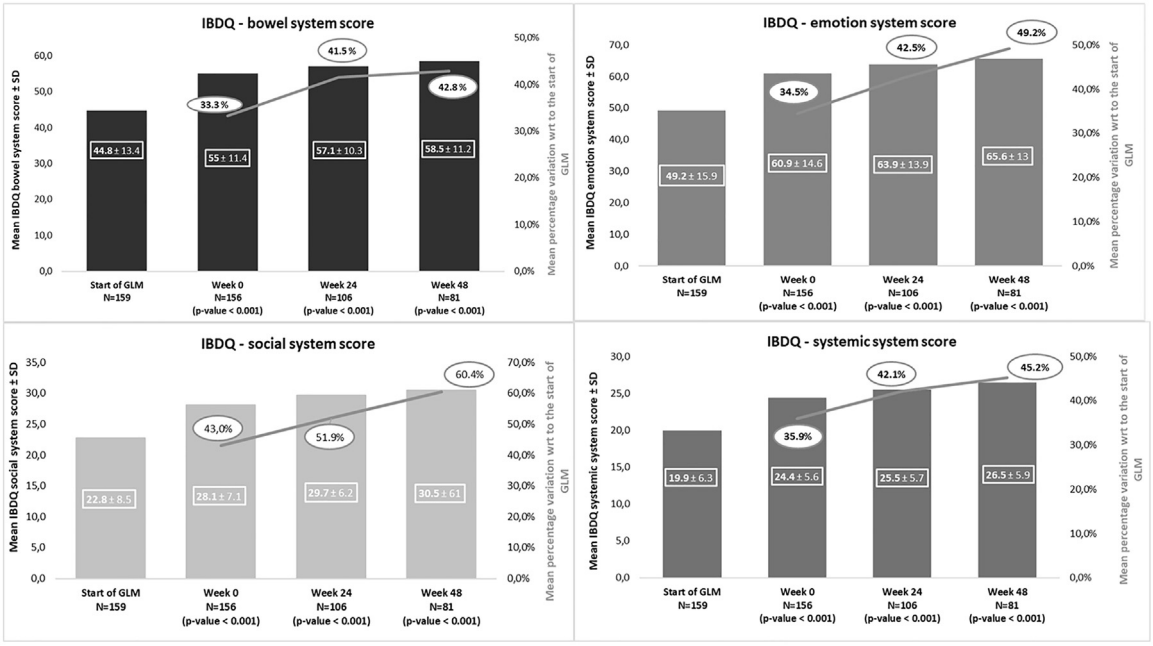

Fig. 4. IBDQ mean subscores (±SD) from the start of GLM therapy to w48. IBDQ = Inflammatory Bowel Disease Questionnaire. SD = Standard Deviation. GLM = Golimumab w48 = Week 48.

Patients with FMS above the median value, at the start of GLM therapy, had 3-fold higher tendency to attain an IBDQ improvement at w24 compared to those with low baseline FMS (OR = 3.580; p-value = 0.004) (Supplementary Table S-2). At w0 and w48 the FMS predictor was not statistically significant. No other analyzed predictors resulted significantly associated with the IBDQ improvement.

Results from simple linear regression found the predictor sex significant at w24 and w48 (p-value = 0.008 and p-value = 0.046 respectively). At both time points the linear regression coefficient for female is negative (−16.647 at w24 and −15.366 at w48), suggesting that the IBDQ score tends to be higher in males (i.e., females tend to have a worse health status). Although the variable sex had an impact on the unitary improvement of the total mean of the IBDQ score in the linear regression model, no significance was found when this variable was analyzed through the logistic model as a predictor of the categorized IBDQ improvement (with respect to the cut-off of 16 points).

3.7. Biomarkers of inflammation

Mean CRP levels (±SD) decreased from 11.8 (±42.2) mg/L at the start of GLM therapy to 7.4 (±33.8) mg/L at w0, 4.1 (±8.1) mg/L at w24 and 3.6 (±9.3) mg/L at w48 (Supplementary Fig. S-1).

Similarly, mean ESR (±SD) decreased from 25.3 (±19.9) mm/h at the start of GLM therapy to 17.2 (±15.3) mm/h at w0, 16.7 (±18.3) mm/h at w24 and 14.9 (±13.3) mm/h at w48 (Supplementary Fig. S-2). The mean change of ESR between w48 and the start of GLM therapy was statistically significant (p-value < 0.001).

3.8. Use of oral corticosteroids (CCS)

The proportion of patients who were receiving concomitant oral corticosteroid decreased from 20.8% (33/159) at the start of GLM therapy, to 10.7% (17/159) at w0 and to 4.4% (4/90) at w48.

At w0 among the 17patients that received concomitant oral corticosteroid 11 were also in clinical remission by PMS; whereas at w48 2 of the 4 patients that received concomitant oral corticosteroid was also in clinical remission by PMS.

3.9. Adverse events

Nine adverse events occurred during the study, 7 of which were considered serious (1 Gastrointestinal disorders, 3 Infections and infestations, 2 Neoplasm benign, malignant and unspecified and 1 Renal and urinary disorders) and 6 potentially drug-related. Five patients discontinued GLM therapy due to adverse events.

Regarding the outcome of these adverse events at the end of the observation period, 4 events were not resolved, 3 were resolved and 2 were still ongoing. None of these adverse events was fatal.

4. Discussion

In recent years, one of the goals of therapeutic interventions in UC has been increasingly focused on the improvement of patients' quality of life, particularly with respect to disease symptoms and adverse events. Accordingly, evaluations of therapy success

include HRQoL measurement tools that can accurately capture what patients consider meaningful to them [3,7].

Among such tools, the Inflammatory Bowel Disease Questionnaire (IBDQ) [34] has proven to be among the most accurate, featuring reliable measurement properties for capturing the psychosocial and clinical variables impacting patients with UC [20,21].

An increasing number of studies have been investigating the impact of treatment on HRQoL of patients with UC; however, reports on GLM therapy are still limited.

The main goals of our study were to assess the impact of GLM therapy on HRQoL, as measured by IBDQ, and on clinical effectiveness in patients with moderate-to-severely active UC, as well as to identify predictors of IBDQ improvement. In our study, IBDQ total scores significantly improved in 61.6% of patients at the end of induction (w0), in 70.8% at w24 after 24 weeks and in 75.3% at w48, increasing on average by 31.4, 31.5 and 46.4 points, and reaching mean values of 168, 178 and 182 points, respectively.

Overall, these findings are consistent to those of other real-life studies that used IBDQ to assess HRQoL and confirm the positive impact of GLM therapy in patients with UC. A study from UK [25] reported that mean IBDQ total score increased in 72.8% of patients at the end of induction, with a mean change of 45.2 points from baseline, and increased to 186.2 points, with a mean change of 66.8, at 54 weeks of golimumab treatment. A study from Greece [30] reported HRQoL improvement at 6 and 12 months in around 75% of patients, with a mean IBDQ total score of 190.5 points at 12 months and a mean change, from baseline, of 40.5 points at 6 months and of 52.9 points at 12 months. According to IBDQ scores, normal QoL-as measured by IBDQ and by EuroQol Group 5 Dimensions Health Questionnaire (EQ-5D) – was achieved by 50% of patients at week 54 in the study of Probert et al. [25] and around 77% of those attending the 12-month visit in the study of Gatopoulou et al. [30]. Finally, a German study [31] reported an overall mean increase in total IBDQ score of 26.5 points after 3 months of treatment with golimumab, and of 41.4 points after 24 months. Of note, the first two studies enrolled only patients naive to biologics, while the German enrolled both naive and biologic-experienced patients, although the authors did not report separate results in these two sub-groups. In our study, results confirm that the improvement of HRQoL is higher in UC patients naïve to anti-TNF compared to those anti-TNF-experienced.

Our study also shows a linear increase of the IBDQ domain subscores, with greatest improvement observed for the domains referring to emotional status and bowel symptoms. These findings provide evidence that GLM therapy improves multiple aspects influencing HRQoL of UC patients. In particular, the improvement of extra-bowel domains is very relevant as many studies demonstrated that the impairment of HRQoL is also influenced by several extra-intestinal factors, such as fatigue and anxiety, which may be present even when UC is in clinical remission [17].

Indeed, achievement of clinical goals may not always fulfill the patients' global needs. For example, treatments that may be effective in terms of clinical remission in the long-term, may not work with the patient's occupational and social life, or may be accompanied by side effects that the patient is unable to tolerate [33].

In the present study we also specifically investigated predictors of HRQoL improvement. Some studies previously identified factors predictive of effectiveness of GLM therapy: short disease duration [37], disease extent [25], clinical response at induction [29], high full Mayo score and non-exposure to anti-TNFs [38]. However, no studies specifically searched for predictors of HRQoL improvement. Our study shows that patients with higher baseline PMS had a 2-fold higher tendency for improving IBDQ at the end of induction, a 5-fold higher tendency to improve the IBDQ at w24 of treatment and a 3-fold higher tendency to attain IBDQ improvement at w48 of treatment compared to those with low baseline PMS. Similarly, patients with higher baseline FMS had 3-fold higher tendency to attain IBDQ improvement at w24 of treatment compared to those with low baseline FMS. These findings are consistent with those of Bossa et al. [38], which showed that a higher total Mayo score was also predictive of a favourable response to GLM. Taken together, these results suggest that in UC patients treated with golimumab, a higher degree of disease activity at baseline may be associated with better clinical effectiveness and HRQoL improvement. We may speculate this result reflects a perception of greater HRQoL psychological wellbeing and satisfaction towards treatment by those patients who had worse clinical scores at baseline.

In this study, we also assessed effectiveness of golimumab by means of disease activity indices and biomarkers. In general, patients showed a marked improvement of disease activity indices within the first 6 weeks of induction and maintained a sustained response throughout the rest of the observation period. Our data also showed a decrease of levels of serum biomarkers associated with disease activity. CRP and ESR dropped from 11.8 mg/l and 25.3 mm/h at GLM starting therapy to 3.6 mg/L and 14.9 mm/h at w48, respectively. Hence, GLM treatment led to improvement of disease activity, documented by reduction of FMS and PMS as well as CRP and ESR. Overall, data about effectiveness of golimumab therapy are in line with those from other previous real-world studies, including a higher rate in terms of clinical response and remission in patients with UC who are naïve to biologics compared to those biologic-experienced [25,27–30,38]. In literature, the impact of medical treatments for UC and specifically anti-TNF alfa on HRQoL has been assessed by a few studies. In particular Paschos et al. [20] found that all agents assessed (infliximab, adalimumab, golimumab, vedolizumab or tofacitinib) significantly improved both generic and HRQoL scores at induction level, while evidence on maintenance level was uncertain. Also the Cochrane review [21] comparing infliximab, adalimumab and golimumab had found that patients assigned to TNF-α antagonists were significantly more likely than placebo patients to have improved IBDQ scores at weeks 6 or 8. The authors commented though despite the results being statistically significant, the change in mean IBDQ score was not clinically meaningful (i.e. $>$16 points) as the mean difference between TNF-α and placebo was approximately 14 points. In consideration of such conclusion, it is worth highlighting that the improvements reported in our study were $>$16 points.

One last aspect noteworthy of comment is the decreasing use of steroids over time in our patient population that is compatible with a better control of disease symptoms and a lower inflammatory burden [40]. This is aligned with recommendations to avoid prolonged and unnecessary use of long-term steroid therapy [11,39,41].

The safety profile of GLM therapy was in line with what expected of the TNF class, and no new safety signals were reported. The major strength of our work is that this is the first study that specifically explored baseline characteristics of patients to identify predictors of IBDQ improvement. Moreover, it is a real-life study that enrolled both biologic-naive and biologic-experienced UC patients. The use of the validated IBDQ makes our data comparable across studies, though perhaps the concomitant administration of a generic questionnaire could have provided additional insight. The main limits of our study are represented by the relatively small sample size and by the lack of evaluation of fecal calprotectin, a non-invasive and likely more accurate marker than CRP and ESR for clinical remission and mucosal healing in the UC population [42].

Another limitation of the study is the lack of FU data on patient exiting the study due to discontinuation. In fact, the protocol did not foresee the collection of further data on study participants after GLM discontinuation. Given the high discontinuation rate,

findings might have been biased by the smaller sample size at each time point and incomplete information (such as, for example, the FMS at W48, given that a large portion of patients who did not undergo colonoscopy). .

In summary, golimumab therapy led to meaningful improvements in HRQoL, disease activity and inflammatory biomarkers at the end of induction and after 30 and 54 weeks of treatment in patients with moderate-to-severely active ulcerative colitis, either naive or experienced to anti- TNF-alpha therapy. Our study confirms that disease activity is one of the most important factors that negatively impact HRQoL in patients with UC (including bowel and systemic symptoms, emotional and social function) and shows that the higher the burden of disease activity at baseline, the greater the improvement of HRQoL.

The identification of predictors of HRQoL improvement might provide further directions for making treatment strategies even more effective.

Author contributions

A.A., A.M.G. and T.D.R. were involved in the design of the study and data analysis. All other authors were involved in the enrolment of patients, data collection and contributed to drafting the paper/revising it critically for intellectual content. All authors have read and agreed to the published version of the manuscript.

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The study (protocol number: MK-8259-6045) was approved by the Ethics Committee of the Fondazione Policlinico Gemelli of Rome (Università Cattolica del Sacro Cuore) on 8 October 2015. Local ethics committee approval from all participating centers.

Informed consent statement

All patients provided written informed consent in accordance with existing applicable laws (DL 196/2003). The study was conducted in accordance with the Declaration of Helsinki.

Conflict of interest

Armuzzi A.: Consultant: AbbVie, Allergan, Amgen, Arena, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mylan, Pfizer, Protagonist Therapeutics, Roche, Samsung Bioepis, Sandoz, Takeda. Lecture fees: AbbVie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Eli-Lilly, Falk, Ferring, Galapagos, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Tigenix

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Saibeni S.: Advisory board, lecture fees, consultancy for: AbbVie, Arena, Janssen, Ferring, Gilead, MSD, Takeda

Scaldaferri F.: MSD, Jansen, Takeda, Sandoz, Ferring, Pfizer

Geccherle A.: Served as a speaker, and/or advisory board member for the following organisations: AbbVie, Takeda, Janssen.

Soriano A.: served as speaker and/or consultant and/or advisory board member and/or received fees from Janssen, Takeda, Pfizer, Novartis.

Orlando A.: AO received lecture grants and/or served as an advisory board member for: AbbVie, Biogen, Chiesi, Janssen-Cilag MSD, Galapagos, Pfizer, Samsung Bioepis, Sofar, and Takeda Pharmaceuticals.

Principi M.B.: Advisory boards, lectures fee, for Abbvie, Janssen, Pfizer, MDS,Takeda.

Sarpi L.: MSD

Cappello M: consultant for Takeda, Janssen-Cilag, Galapagos, Ferring, Biogen, speaker for Takeda, Biogen, Janssen-Cilag, Galapagos, Ferring

D'Incà R.: Advisor for MSD, Takeda, Janssen, Biogen Lecture fees: Galapagos

Bossa F.: Advisory board per Janssen; Pfizer; Celgene; Galapagos; Takeda

Bezzio C.: received lecture fees and served as a consultant for Takeda, MSD, Ferring, Galapagos and Janssen.

Data availability

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. The datasets generated during or analyzed during the current study are not publicly available. All data used in this study were anonymized to respect the privacy of patients in line with applicable laws and regulations.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.07.031.

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