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The effects of golimumab on patient centric outcomes amongst rheumatoid arthritis patients in Greece. The GO-Q study

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Abstract

This study aimed at assessing the impact of golimumab on health-related quality of life (HRQoL) and other patient-reported outcomes (PROs) in patients with rheumatoid arthritis (RA) in real-world settings. GO-Q was an observational, prospective, 12-month study, which recruited patients with moderate-to-severely active RA initiating golimumab treatment per label in rheumatology clinics and private practices. Primary endpoint was the change in PROs [EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) questionnaire, Health Assessment Questionnaire Disease Index (HAQ-DI), and Work Productivity and Activity Index for RA (WPAI:RA)] after 12 months of treatment. Other endpoints included Disease Activity Score for 28 joints with erythrocyte sedimentation rate (DAS28-ESR), healthcare resource utilization, and golimumab adherence. Changes in continuous variables from baseline were evaluated with the paired *t* test. One hundred forty-five patients were recruited. The mean [standard deviation (SD)] EQ-5D-3L index increased significantly at 12 months versus baseline [from 0.427 (0.206) to 0.801 (0.229); $p < 0.0001$], with changes as early as 3 and 6 months (both $p < 0.0001$). Accordingly, there were statistically significant changes in all WPAI:RA domains from baseline to 3, 6, and 12 months ($p < 0.0001$). Patients' function improved gradually from the third month until the end of follow-up ($p < 0.0001$ for all time-points). Thirty (27.3%) and 60 (54.6%) patients achieved remission (DAS28-ESR < 2.6) and low disease activity (DAS28-ESR ≤ 3.2), respectively, at 12 months. Adherence rate to golimumab was high (mean [SD] 90.3% (7.5) at 12 months). In patients with moderate-to-severely active RA, golimumab significantly improved HRQoL, physical function, and work productivity and activity, with improvements in disease activity over 12 months in real-world settings.

Keywords Golimumab · Rheumatoid arthritis · Health-related quality of life · Patient-reported outcomes · Effectiveness · Real-world study

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic disease associated with inflammatory activity and joint damage [1]. Significant developments in the management of patients with RA have been accomplished over the past decades, including the application of treat-to-target therapy, aiming at sustained remission or low disease activity (LDA) as the best possible alternative [2, 3]; the development of validated, reliable, physician-derived metrics for the assessment of disease activity [4]; and the development of patient-reported outcomes (PROs) to measure the physical, emotional, and

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social burden of RA [5, 6]. In parallel, the likelihood of achieving remission or LDA in everyday clinical practice was also improved with the advent of newer therapies than the conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs), such as the biologic (b) and the targeted synthetic (ts) DMARDs [3]. Nevertheless, the development of new RA treatments is ongoing, with several new antibodies targeting pro-inflammatory mediators (e.g., granulocyte–macrophage colony-stimulating factor) or modulating anti-inflammatory cytokines (e.g., interleukin [IL]-2 and IL-10) currently being assessed in clinical trials [7].

Despite the significant progress in RA management, many patients do not achieve remission or LDA, even with the newer bDMARDs or tsDMARDs [8, 9]. In our most recent longitudinal 5-year analysis of Greek nationwide data of RA patients treated with bDMARDs, we found that only 23% of patients have persistent (> 50% of the time) LDA or remission, while the majority (77%) remain in a persistent moderate disease state [10].

Recent advances in treatment for RA have reduced the clinical signs of the disease, such as joint damage and disease activity markers, in many patients. However, health-related quality of life (HRQoL) can still be sub-optimal in patients without clinical signs of active disease and may indicate an unmet need [11]. Patients with RA experience significant impairment in HRQoL due to pain, deficits in physical function, sleep disturbances, and fatigue associated with the disease [12, 13]. In fact, physical function is the most affected HRQoL domain in patients with RA than in the general population [14]. Therefore, sustaining HRQoL is of primary importance in patients with RA, especially for those who do not attain their treatment targets [11]. Towards this end, PROs provide information on treatment efficacy from the patient's perspective and represent a simple and effective method of collecting important long-term data from patients with RA treated in everyday settings [15].

Golimumab is a human monoclonal antibody that prevents the binding of tumor necrosis factor (TNF) α to its receptors [16]; in the European Union, golimumab at 50 mg monthly doses (or 100 mg for patients with a body weight > 100 kg who do not achieve an adequate clinical response after 3 or 4 doses of 50 mg per month) is approved in combination with methotrexate for the treatment of adult patients with moderate-to-severe active RA and an inadequate response to DMARDs, or adult patients with severe, active, and progressive RA not previously treated with methotrexate. Golimumab's efficacy and safety have been shown in several pivotal randomized clinical trials, including in patients with RA and an inadequate response to methotrexate, in whom golimumab combined with methotrexate significantly improved the physical function, general health, and fatigue [17–20]. Additionally, a retrospective database analysis with up to 7 years of follow-up of the Spanish BIOBADASER registry has found a high probability of persistence with golimumab, and lower risk of treatment discontinuation in patients receiving golimumab as their first biological treatment [21, 22]. At present, limited real-world data are available on the impact of golimumab on HRQoL and other PROs [23–25] or on disease activity [27–29] in patients with RA.

Therefore, this study aimed to investigate the association of golimumab use with HRQoL and other PROs in patients with moderately-to-severely active RA in real-world settings over 12 months. Additionally, we assessed the impact of golimumab on disease activity and healthcare resource utilization, and the adherence to golimumab therapy during follow-up.

Methods

Study design, patients, and treatment details

GO-Q was an observational, prospective, uncontrolled, 12-month cohort study conducted in 22 rheumatology sites across Greece from March 2017 to February 2019. The planned study follow-up period was 12 months, and four visits were expected to be held, as per routine clinical practice, the first one being at enrollment (baseline) and the remaining at approximately 3, 6, and 12 months. Data from patients who attended fewer than all four visits were also included in the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by each center's institutional review board or ethics committee. All subjects provided written informed consent before study entry.

Eligible patients were 18 years or older who were diagnosed with RA based on the 1987 American College of Rheumatology criteria [30]. At baseline, patients had moderately-to-severely active RA, defined as a Disease Activity Score of 28 joints with the use of the erythrocyte sedimentation rate (DAS28-ESR) of > 3.2 [31], who had not received previous treatment with golimumab. The decision to initiate golimumab, either as the first or the second bDMARD, was made by the treating physician before and independently from the decision to include the patient in the study. The criteria for exclusion included previous treatment with > 1 bDMARDs for any rheumatic disorder; switching TNFs due to primary non-response or any safety-related event (e.g., infection); moderate or severe heart failure (New York Heart Association class III/IV); tuberculosis or other severe infections, including sepsis, abscesses, and opportunistic infections; current or past (within the previous year) history of alcohol or drug abuse; and hypersensitivity to the active compound or any of the excipients of golimumab, and hypersensitivity to other murine proteins.

All included patients were prescribed subcutaneous golimumab as per label [16]. Golimumab treatment could be discontinued at the investigator's discretion or the patient's preference. Concomitant medications for RA, including background csDMARDs, were permitted.

Study assessments and definitions

Investigators recorded all relevant study data at baseline, 3, 6, and 12 months using an electronic case report form. Patients were requested to record information regarding golimumab treatment, PROs, and healthcare resource utilization in a diary. Data recorded at baseline included demographic characteristics and clinical history. PROs, medications for RA, and clinical examinations were recorded at baseline, 3, 6, and 12 months. Healthcare resource utilization data were collected at 3, 6, and 12 months.

Quality of life was assessed with the self-reported EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) [32–34]. The EQ-5D-3L consists of a descriptive profile of the respondent's health state and a self-rated current health visual analog scale (EQ-VAS). The EQ-5D-3L health states, resulting from the descriptive system, can be converted into a single index value using the UK population weighting to normalize it to a given population; index values range from 0 (death) to 1 (perfect health). Physical function was measured with the Greek version of the Health Assessment Questionnaire-Disability Index (HAQ-DI), a patient-reported questionnaire specific to RA [35]. Work productivity and activity impairment were assessed using the validated Greek version of the self-reported Work Productivity and Activity Impairment in Rheumatoid Arthritis (WPAI:RA) questionnaire [36].

Disease activity was measured with the DAS28-ESR [37] and the European League Against Rheumatism (EULAR) response criteria [31]. Remission was defined as DAS28-ESR < 2.6, LDA as DAS28-ESR ≤ 3.2, and high disease activity as DAS28-ESR > 5.1 [31]. The impact of golimumab treatment on the use of concomitant RA-related treatments and healthcare resource utilization was based on the analysis of the patients' diary. Data on RA-related treatments, e.g., csDMARDs, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids, included the type of medication and posology. Data on healthcare resource utilization included medication, hospitalizations (all-cause and RA-related), and visits in daycare and outpatient settings.

The adherence to golimumab therapy was calculated by dividing the total number of golimumab injections dispensed by the scheduled number of golimumab injections over 12 months; rates $\geq 80.0\%$ were defined as high adherence rates. Data for calculating adherence rates and reasons for low golimumab adherence or discontinuation were extracted from the patients' diaries as applicable.

Endpoint measures

The primary endpoint measures were the frequency distribution of the EQ-5D-3L dimension responses, the mean EQ-VAS score, and EQ-5D-3L index value at each visit.

The secondary endpoints assessed the mean change in the HAQ-DI and the WPAI:RA domain scores from baseline to each consecutive visit; the mean change in the DAS28-ESR from baseline to each consecutive visit; the proportions of patients achieving remission and LDA according to DAS28-ESR, and treatment response according to the EULAR response criteria from baseline to each consecutive visit; the proportion of patients achieving treatment response based on DAS28-ESR reduction of ≥ 1.2 or decrease to ≤ 3.2 at each follow-up visit; the health care resource utilization, by recording the type and number of visits to health care facilities and medical interventions; and, finally, the proportion of patients on golimumab treatment at the end of 12 months and the description of reasons for discontinuations.

Statistical analysis

All analyses used the full analysis set of patients (i.e., all patients who received ≥ 1 dose of golimumab and fully completed the baseline EQ-5D-3L questionnaire). Descriptive analyses were performed for all study data. Categorical variables were displayed as frequency tables (*N*, %), and continuous variables with mean values and standard deviation [SD] or median interquartile range (IQR). Association between categorical variables was assessed using the chi-square test. Differences in the mean values of continuous variables at different time periods were analyzed with the paired *t* test. No imputations of the missing PRO measurements were used. Medical history, comorbidities, and safety events were coded using the Medical Dictionary for Regulatory Activities (MedDRA); system organ class and preferred terms were tabulated in frequency tables (*n*, %). Previous RA-related therapy and concomitant medications were coded using the Anatomical Therapeutic Chemical (ATC) Classification System by the World Health Organization Collaborating Centre for Drug Statistics Methodology and were presented in frequency tables. All statistical tests were two-sided and were performed at a 0.05 significance level. The analysis was carried out with SAS® 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline demographic and clinical characteristics

In total, 145 patients were enrolled. The patients' baseline demographic and clinical characteristics are shown in Table 1. The median (IQR) time from RA diagnosis to the

baseline of this study was 2.7 (4.6) years. The proportions of patients who were positive for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (aCCP) were 45.5% and 37.9%, respectively. Overall, patients had severe disease activity (mean [SD] DAS28-ESR score of 5.4 [0.9]). Before study entry, 127 (87.6%) patients had been treated for RA with csDMARDs; the most frequently used csDMARDs were methotrexate (in 118/145 patients, 81.4%) followed by leflunomide (in 47/145 patients, 32.4%). Corticosteroids, NSAIDs, and bDMARDs (maximum of one due to exclusion criteria) were received by 101 (69.7%), 24 (16.6%), and 31 (21.4%) patients, respectively. At baseline, 69 (47.6%) patients presented with comorbidities; a total of 152 comorbid conditions were reported, the most frequent being osteoporosis (23.7%), hyperlipidemia (13.2%), and hypertension (10.5%).

Patient disposition and treatment details during follow-up

The numbers of patients attending the 3-, 6-, and 12-month visits were 135 (93.1%), 132 (91.0%), and 110 (75.9%), respectively. Most patients were treated with golimumab 50 mg monthly doses (1,514/1,523 administrations, 99.4%). The remaining 9 administrations (9/1523 administrations, 0.6%; corresponding to 2 patients) were golimumab 100 mg, per label.

The impact of golimumab on HRQoL and other PROs

The patients' frequency distribution of EQ-5D-3L dimension responses at baseline, 3, 6, and 12 months is shown in Table 2. Compared to baseline, sequentially increasing proportions of patients reported having 'no problems' in all dimensions at 3, 6, and 12 months. The mean (SD) EQ-VAS scores at baseline, 3, 6, and 12 months were 47.6 (16.8), 62.8 (21.2), 66.8 (21.6), and 77.4 (16.8), respectively. The mean (SD) EQ-5D-3L index values at baseline, 3, 6, and 12 months were 0.427 (0.206), 0.641 (0.236), 0.711 (0.224) and 0.801 (0.229), respectively. Overall, the mean (SD) changes in the EQ-5D-3L index values from baseline to 3, 6, and 12 months were 0.21 (0.24), 0.28 (0.25), and 0.38 (0.30), respectively ($p < 0.0001$ all comparisons; Fig. 1).

The mean (SD) HAQ-DI score at baseline, 3, 6, and 12 months was 1.45 (0.61), 0.88 (0.67), 0.71 (0.57), and 0.48 (0.46), respectively. The mean (SD) changes in the HAQ-DI score from baseline to 3, 6, and 12 months were -0.58 (0.53), -0.75 (0.62), and -1.04 (0.73), respectively ($p < 0.0001$, all comparisons; Fig. 2). No statistically significant differences were seen between biological-experienced and biological-naïve patients in the HAQ-DI score at baseline or at each of the follow-up visits (data not shown).

Most patients (131/145, 90.3%) were in paid employment at baseline. Of patients with available information at 3, 6, and 12 months, employed patients were 119/133 (89.5%), 110/130 (84.6%), and 90/109 (82.6%), respectively. The mean scores for each WPAI:RA domain were reduced

Table 1 Patient demographic and clinical characteristics at baseline[a]

Characteristics	All patients ($N = 145$)
Demographic characteristics	
Age, years	54.6 (12.2)
Female sex, *n* (%)	116 (80.0)
Smoking status, *n* (%)	
Never	108 (74.5)
Current	29 (20.0)
Past	7 (4.8)
Duration of RA from diagnosis to study enrolment, years, median (IQR)	2.7 (4.6)
Clinical characteristics	
Positive for rheumatoid factor, *n* (%)	66 (45.5)
Positive for anti–cyclic citrullinated peptide, *n* (%)	55 (37.9)
Bone erosions[b]	5.8 (5.6)
Swollen-joint count, of 28 joints examined	8.7 (4.4)
Tender-joint count, of 28 joints examined	10.1 (4.3)
C-reactive protein, mg/L, median (IQR)	3.0 (11.3)
Erythrocyte sedimentation rate, mm/h, median (IQR)	26.0 (33.0)
DAS-28 ESR	5.4 (0.9)
Patients with comorbidities, *n* (%)	69 (47.6)
Previous treatments, *n* (%)[c]	
Biological DMARDs	31 (21.4)
Conventional synthetic DMARDs	127 (87.6)
Corticosteroids	101 (69.7)
NSAIDs	24 (16.6)
Biological DMARDs, *n* (%)	
Adalimumab	8 (5.5)
Etanercept	7 (4.8)
Abatacept	6 (4.1)
Tocilizumab	6 (4.1)
Infliximab	3 (2.1)
Certolizumab pegol	1 (0.7)

Data are mean (SD) unless otherwise indicated

DAS28 disease activity score for 28 joints, *DMARD* disease-modifying antirheumatic drug, *ESR* erythrocyte sedimentation rate, *IQR* interquartile range, *N* total number of patients, *n* number of patients in the specified group, *NSAID* nonsteroidal anti-inflammatory drug, *RA* rheumatoid arthritis, *SD* standard deviation

[a]Not all patients had available data for all parameters

[b]Twenty-one patients presented with bone erosions

[c]Patients may have received multiple agents

Table 2 Frequency distribution for each of the EQ-5D-3L dimension at baseline, 3, 6, and 12 months

	Baseline ($N=144$)[a]	3 months ($N=135$)	6 months ($N=131$) [a]	12 months ($N=110$)
Mobility, *n* (%)				
I have no problems walking about	27 (18.8)	69 (51.1)	89 (67.9)	89 (80.9)
I have some problems walking about	113 (78.5)	63 (46.7)	41 (31.3)	21 (19.1)
I am confined to bed	4 (2.8)	3 (2.2)	1 (0.8)	–
Self-care, *n* (%)				
I have no problems with self-care	37 (25.7)	81 (60.0)	94 (71.8)	90 (81.8)
I have some problems washing or dressing myself	98 (68.1)	51 (37.8)	37 (28.2)	20 (18.2)
I am unable to wash or dress myself	9 (6.3)	3 (2.2)	–	–
Usual activities, *n* (%)				
I have no problems with performing my usual activities	9 (6.3)	61 (45.2)	76 (58.0)	79 (71.8)
I have some problems with performing my usual activities	126 (87.5)	70 (51.9)	55 (42.0)	31 (28.2)
I am unable to perform my usual activities	9 (6.3)	3 (2.2)	–	–
Not answered	–	1 (0.7)	–	–
Pain/discomfort, *n* (%)				
I have no pain or discomfort	4 (2.8)	45 (33.3)	58 (44.3)	73 (66.4)
I have moderate pain or discomfort	102 (70.8)	84 (62.2)	70 (53.4)	34 (30.9)
I have extreme pain or discomfort	38 (26.4)	6 (4.4)	3 (2.3)	3 (2.7)
Anxiety/depression, *n* (%)				
I am not anxious or depressed	28 (19.4)	55 (40.7)	68 (51.9)	68 (61.8)
I am moderately anxious or depressed	80 (55.6)	63 (46.7)	49 (37.4)	36 (32.7)
I am extremely anxious or depressed	36 (25.0)	17 (12.6)	14 (10.7)	6 (5.5)

EQ-5D-3L EuroQol-5 dimensions-3 levels, *N* total number of patients

[a]At baseline and at 6 months, one of the included patients did not answer the EQ-5D-3L instrument

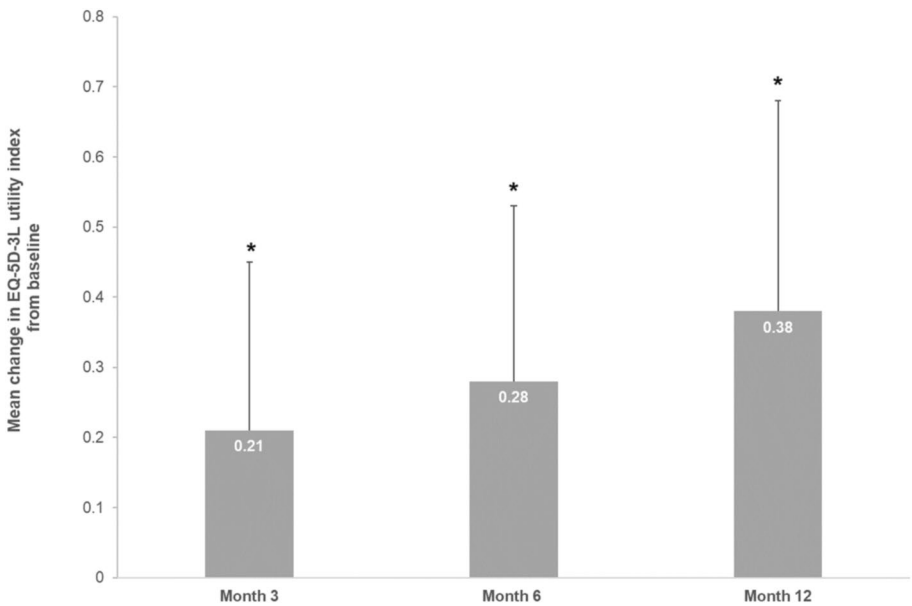

Fig. 1 Mean change in the EQ-5D-3L index value from baseline to 3, 6, and 12 months. T bars denote the standard deviation. *$p<0.0001$, obtained with the paired *t* test. *EQ-5D-3L* EuroQol-5 dimensions-3 levels

from baseline through to 12 months (see Supplementary Appendix S1). The mean (SD) changes for all WPAI:RA domain scores from baseline to 3, 6, and 12 months were statistically significant ($p<0.0001$ all comparisons; Fig. 3). No statistically significant differences were seen between biological-experienced and biological-naïve patients in WPAI:RA domain scores at baseline or at each of the follow-up visits, except for presenteeism and work productivity

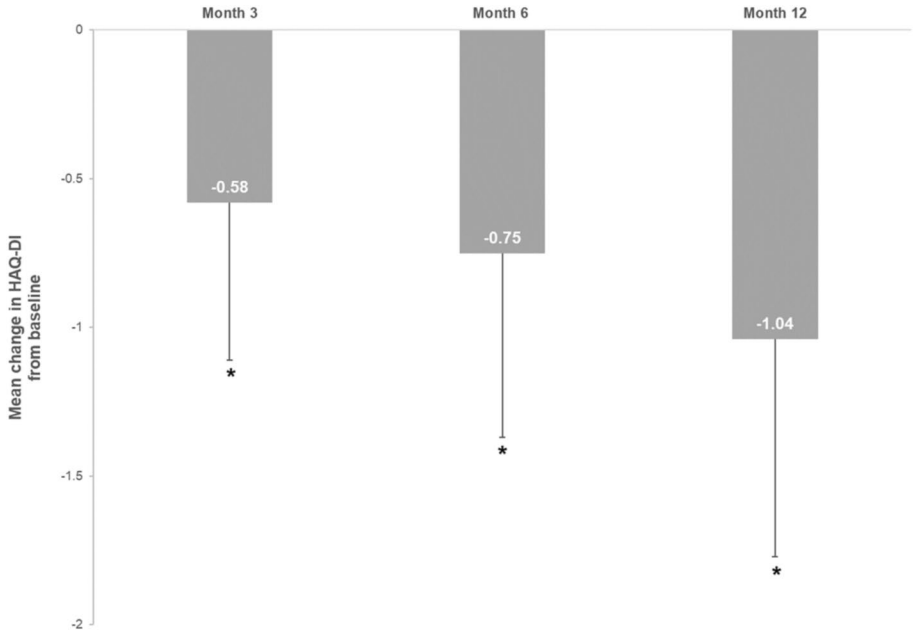

Fig. 2 Mean change in the HAQ-DI score from baseline to 3, 6, and 12 months. T bars denote the standard deviation.*$p < 0.0001$, obtained with the paired *t* test. *HAQ-DI* health assessment questionnaire—disability index

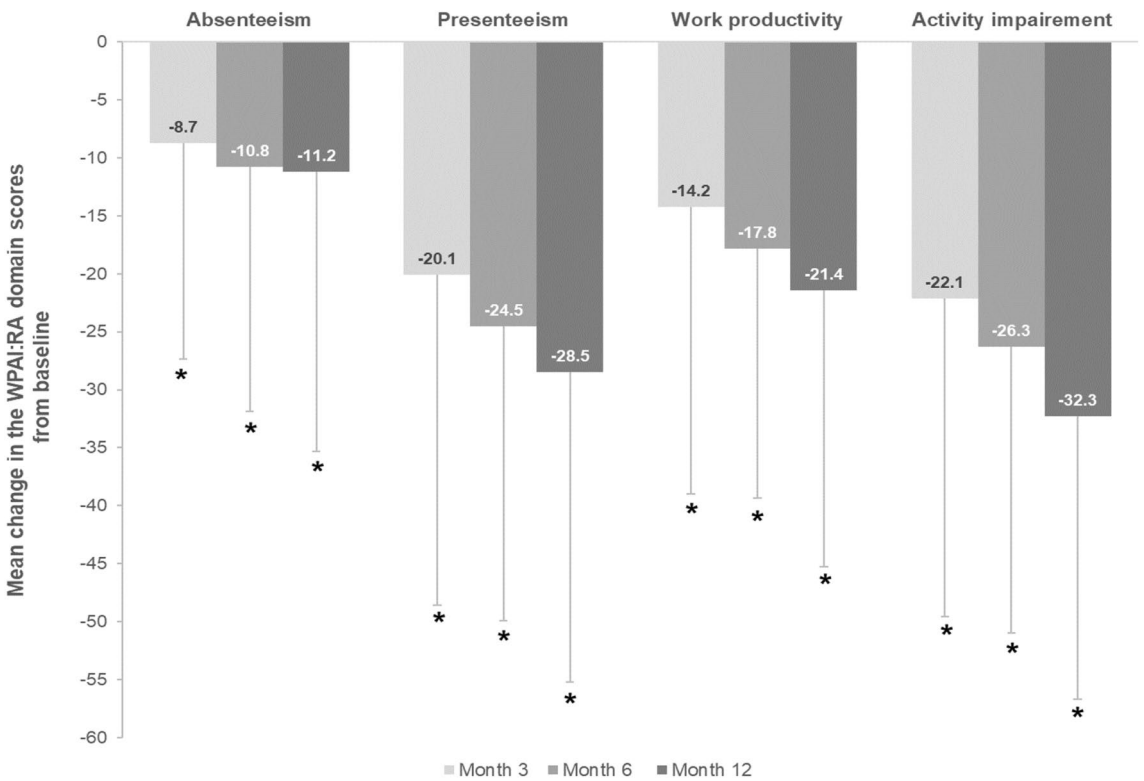

Fig. 3 Mean change in the WPAI:RA domain scores from baseline to 3, 6, and 12 months. T bars denote the standard deviation. *$p < 0.0001$, obtained with the paired *t* test. *WPAI* work productivity and activity impairment, *RA* rheumatoid arthritis

at 6 months, albeit the difference was marginal in the latter domain ($p = 0.042$ and $p = 0.051$, respectively; data not shown).

Impact of golimumab on disease activity, concomitant RA-related medications, and healthcare resource utilization

Disease activity significantly improved at 3, 6, and 12 months compared to baseline, with mean (SD) DAS28-ESR scores of 4.1 (1.2), 3.7 (1.2), 3.2 (1.1), and 5.4 (0.9), respectively ($p < 0.0001$, all comparisons) (Fig. 4). Of patients attending the 3-, 6-, and 12-month visits, the proportions achieving remission were 13.3%,18.9%, and 27.3%, respectively; the proportions achieving LDA were 24.4%, 35.6%, and 54.6%, respectively; the proportions achieving treatment response based on a DAS28-ESR reduction of ≥ 1.2 were 49.6%, 57.6%, and 76.4%, respectively; and, finally, the proportions achieving good EULAR response were 22.2%, 31.8%, and 48.2%, respectively (see Supplementary Appendix S2). No statistically significant differences were seen between biological-experienced and biological-naïve patients in terms of DAS28-ESR score development, or moderate or good EULAR response at the follow-up visits (data not shown).

All patients (145, 100.0%) received csDMARDs during follow-up, with the majority of patients receiving a single agent (120, 82.8%). The most frequently prescribed csDMARDs were methotrexate (130/145 patients, 89.7%) and leflunomide (27/145 patients, 18.6%). The mean (SD) methotrexate dose was 15.1 (5.1) mg per week. Of all patients, those receiving corticosteroids or NSAIDs along with golimumab were 81 (55.9%) and 14 (9.7%), respectively. Of patients receiving corticosteroids, most received only a single agent (76, 93.8%). Overall, compared to the period before study entry, during follow-up, numerically smaller proportions of all patients received corticosteroids (69.7% and 55.9%, respectively) or NSAIDs (16.6% and 9.7%, respectively).

Almost all patients attending the visits at 3, 6, and 12 months reported having utilized healthcare resources for RA-related reasons since the previous visit (3 months: 130 [96.3%]; 6 months: 123 [92.3%]; 12 months: 107 [97.3%]). Most patients reported having performed laboratory tests (3 months: 129 [99.2%]; 6 months: 117 [95.1%]; and 12 months: 102 [95.3%]). ESR, C-reactive protein levels, complete blood count, and other biochemical markers were the most common tests. Imaging tests and biopsies were reported by a total of seven patients. No hospitalizations were reported.

Adherence rate and discontinuations with golimumab treatment

The mean (SD) adherence rate during the follow-up period was 90.3% (7.5). No statistically significant difference in the mean adherence rate was observed between biological-experienced and biological-naïve patients ($p = 0.152$; data not shown). Of all study patients, 35 (24.1%) discontinued golimumab treatment before the end of the follow-up period;

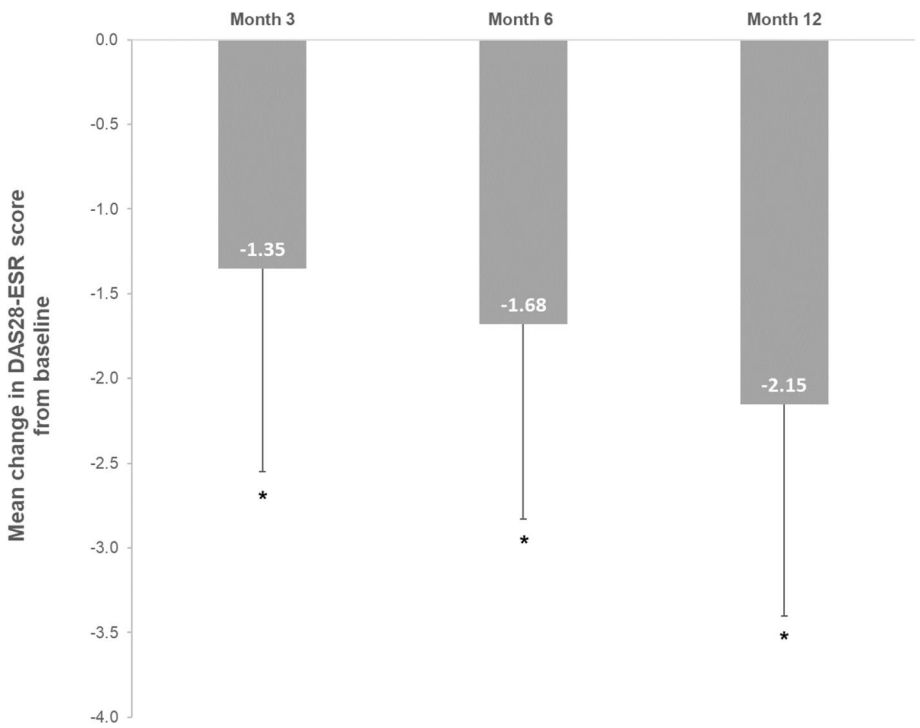

Fig. 4 Mean change in the DAS28-ESR score from baseline to 3, 6, and 12 months. T bars denote the standard deviation. *$p < 0.0001$, obtained with the paired *t* test. *DAS28* disease activity score, 28 joint counts, *ESR* erythorcyte sedimentation rate

of these, 14 (40.0%) patient discontinuations were associated with drug ineffectiveness and 11 (31.4%) patients discontinued due to early study termination resulting from the death of the investigator. Other reasons for discontinuation included lost to follow-up (8 patients; 22.9%), withdrawal of consent (1 patient; 2.9%), and patient's choice (1 patient; 2.9%).

Discussion

GO-Q was a non-interventional, prospective, 12-month cohort study that assessed the impact of golimumab on HRQoL and other PROs in patients with moderate-to-severe RA, despite previous treatment with csDMARDs and/or one bDMARD. Furthermore, the study assessed the impact of golimumab on disease activity, healthcare resource utilization, and adherence to golimumab therapy.

The primary study finding was that golimumab improved the patients' HRQoL. Compared with baseline, continuous numerical increases were observed in the proportions of patients reporting 'no problems' in all EQ-5D-3L descriptive domains at 3, 6, and 12 months. Of note, a substantial numerical increase from baseline to 12 months was observed in the proportion of patients reporting 'no pain/discomfort' (2.8% to 66.4%, respectively); this finding is important, as pain control is the most frequent patient priority during a rheumatology clinic visit [38]. Improvements from baseline to 12 months were also seen in the patients' self-reported health (mean EQ-VAS score from 47.6 to 77.4, respectively) and overall health (mean EQ-5D-3L index value from 0.427 to 0.801, respectively; $p < 0.0001$). These HRQoL improvements are overall consistent with the findings of the real-world GO-NICE study in patients with RA who received golimumab for 24 months [24]. In GO-NICE, statistically significant decreases were seen in the proportions of patients reporting some or extreme problems in all EQ-5D-3L domains already by 6 months, which were then sustained throughout the observation period. Furthermore, as with the current study, GO-NICE reported a statistically significant improvement in the patients' mean EQ-VAS score from baseline to 12 months (51.0–62.4, $p < 0.0001$).

Another finding of the present study was that golimumab improved the functional status of patients with RA, with the mean HAQ-DI score being reduced from 1.45 at baseline to 0.48 at 12 months; in fact, the HAQ-DI score at 12 months was below the cutoff point of 0.5, which indicates normal physical function [20]. Furthermore, as compared to baseline, the improvements in the patients' functional status were significant ($p < 0.0001$) at 3 months and were sustained throughout the remainder of the follow-up period. Although real-world data are limited in the literature, our results are consistent with findings from the Italian GISEA registry on 302 RA patients [25]. In this registry, the data were analyzed in three groups: biological-naïve, biological-experienced with one prior biologic treatment and biological-experienced with 2 or more prior biologic treatments, providing results that were overall comparable to our study. At 6 and 12 months the HAQ-DI score decreased in the biologic-naïve group and in the biologic-experienced groups versus baseline. However, in contrast to the present study, there was a greater decrease in HAQ-DI at 6 months for biological-naïve patients versus experienced patients but this difference was not seen at 12 months. Furthermore, improvements in functional ability, although assessed with a different questionnaire (Gunktionsfragebogen Hannover; FFbH), were also reported in the real-world GO-NICE study. Although real-world studies such as the current one cannot be compared with randomized clinical trials, the GO-FORWARD randomized clinical trial showed a statistically significant ($p < 0.001$) improvement in the HAQ-DI following 24 weeks of treatment with golimumab 50 or 100 mg and methotrexate versus placebo and methotrexate, which was sustained through to 52 weeks [20].

Finally, golimumab treatment statistically significantly ($p < 0.0001$) improved all WPAI:RA domain scores from baseline to each of the 3-, 6- and 12-month visits, while a non-significant numerical decrease in the proportion of paid employees was observed during the study. Similar improvements in presenteeism, work productivity, and activity impairment with golimumab treatment at 3, 6, and 12 months were reported in the recent GO-ART study [26]. However, in GO-ART, the change in absenteeism from baseline to 6 months was not significant in the subgroup of patients with RA. These differences could be attributed to study design differences between this study and GO-ART, possibly including the patients' baseline demographic and clinical characteristics. GO-ART included patients with RA and other rheumatoid inflammatory diseases; however, the baseline demographic and clinical characteristics are not available for patients with RA only, except from the fact that a numerically higher proportion of patients with RA were biologic-experienced as compared with the present study (31.2% and 21.4%, respectively).

In parallel to PRO improvements, golimumab treatment over 12 months improved the patients' disease activity, with the mean DAS28-ESR score being reduced from 5.4 at baseline to 3.2 at 12 months. Moreover, the mean DAS28-ESR score changes from baseline to each of the follow-up visits were statistically significant ($p < 0.0001$). Similar reductions in disease activity were reported in the GO-NICE study, where the DAS28-ESR score was reduced from 5.0 at baseline to 3.3 after 12 months for all patients ($p < 0.0001$) [28]. Likewise, a recent, retrospective, real-world study in patients with RA initiating golimumab treatment in Japan,

where the median DAS28-ESR score was reduced from 4.3 at baseline to 2.7 at 52 weeks [39]; of note, the latter study showed that the golimumab effectiveness was maintained during a median observation period of 134 weeks. Finally, the present study showed that following 12 months of treatment with golimumab, 27.3% of patients were in remission, 54.6% had LDA, and approximately half of patients had good EULAR response. In contrast, the recent GO-BEYOND real-world study in Turkey reported higher (58.8%) proportions of patients with RA achieving remission at 12 months with golimumab [40]. This between-study difference in the proportions of patients with RA achieving remission at 12 months could be attributed to the different study designs, as well as, the small ($N = 60$) sample size of patients with RA in GO-BEYOND, with only 34 patients been evaluated for disease activity at 12 months.

In terms of RA-related concomitant medications, all patients received concomitant csDMARDs during the follow-up period. However, numerically fewer patients used concomitant corticosteroids or NSAIDs during follow-up as compared with the period before study entry.

In this study, healthcare resource utilization was driven primarily by RA-related laboratory tests, with > 95% of patients reporting such examinations. A low number of patients reported having performed imaging tests/biopsies, while no hospitalizations were reported. The latter finding contrasts the finding from the GO-ART study, where hospitalizations for RA patients were reported and these were decreased by 5.3% during the 2-year golimumab treatment period as compared with the year before study entry [26].

This study showed a high (90.3%) mean adherence rate to golimumab treatment over 12 months, which is greater than expected for the real-world setting. A recent review of adherence to subcutaneous bDMARDS in inflammatory rheumatic or bowel diseases found an adherence range of 28.8–89.4% [41]. Real-world studies of bDMARDS in RA have reported adherence rates of 85.7% in Spain [42], and 34–46% for newly-initiated bDMARDs in the US over 2 years [43]. Finally, in this study, discontinuations over 12 months were observed for 24.1% of all patients, with approximately half of them discontinuing for drug ineffectiveness reasons. By comparison, a retrospective, real-world study conducted in Japan showed that 89.6% of patients with RA were continuing golimumab over a shorter duration (6 months) after initiation treatment [44, 45], while the previously mentioned GO-BEYOND real-world study reported 24-month retention rates of golimumab treatment of 67.2% and 57.1% for biologic-naïve and biologic-experienced patients with RA, respectively [44, 45].

Limitations of this study mainly relate to its observational nature. The possibility of patient selection bias cannot be ruled out, as treatment initiation with golimumab was based solely on the investigator's judgment. Of note, the proportions of patients who were positive for RF (45.5%) and aCCP (37.9%) in this study were relatively lower than those described in the literature (RF, 70–90% [46]; aCCP, 69% [47]). It is generally assumed that seronegative versus seropositive RA is associated with a milder disease course [48]; however, cases of severe, destructive disease in seronegative patients have been reported. The 12-month follow-up period may limit the extrapolation of the results to longer-term, given that RA is a chronic condition. It is also possible that the responses to PROs may have been subject to patient or investigator bias. Investigator bias may be introduced by the possible selective reporting of PRO results [49]. The possibility of patient recall bias may be introduced by the collection of data pertaining to PROs; however, every effort was made to mitigate patient recall bias through the use of PROs validated in the Greek language and with a short-term recall period [49]. Finally, it is possible that the statistical accuracy of the estimation of study outcomes at each timepoint may decrease either due to the number of patients who were lost from follow-up, or from the early termination of 11 patients due to the death of one investigator.

In conclusion, in patients with moderate-to-severely active RA despite previous treatment with csDMARDs and/or one bDMARD, golimumab significantly improved the patients' HRQoL, physical function, and work productivity and activity limitation over 12 months in real-world settings. In parallel to PRO improvements, treatment with golimumab resulted in significant improvements in disease activity. Treatment with concomitant RA medications was high during golimumab treatment, while healthcare resource utilization was low; mainly RA-related laboratory tests. Adherence to golimumab treatment was high.

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Availability of data and material Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study can be submitted through the EngageZone site or via to dataaccess@merck.com.

Code availability All data were analyzed using SAS v9.4 (SAS Institute, Cary, NC).

Declarations

Conflict of interest Dr Dimitrios Vassilopoulos has received honoraria from Abbvie, Janssen, MSD, Novartis, Pfizer, Roche, and UCB. Dr Prodromos Sidiropoulos has received honoraria from AbbVie, Amgen, MSD, Novartis, Pfizer, Roche, and UCB. Dr Evangelia Petrikkou and Dr Achilleas Livieratos are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA, who may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA. For the remaining authors none were declared.

Ethical standards The study was designed and conducted in accordance with the guidelines for Good Pharmacoepidemiology Practice of the International Society for Pharmacoepidemiology, the ethical principles laid down in the Declaration of Helsinki, and all applicable local rules and regulations. The study was approved by the competent Institutional Review Boards of all participating hospital sites. Participation of private practice investigators was approved by the Institutional Review Board of a participating hospital located in the same geographic region as the Private Practice.

Informed consent All persons gave their informed consent prior to their inclusion in the study. All participants provided consent for publication of the material collected in the context of this study in a non-identifiable manner.

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