Real-world effectiveness and safety of golimumab in rheumatoid arthritis treatment: A two-center study in Taiwan

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Abstract

Background: The real-world outcomes of golimumab (GLM) use have been rarely studied in Asian patients with rheumatoid arthritis (RA). This study assessed the real-world effectiveness and safety of GLM in a Taiwanese cohort.

Methods: One hundred and eight GLM-treated RA patients were enrolled. Predictors of a good European League Against Rheumatism (EULAR) response at 24 months and drug retention were identified through multivariate analyses.

Results: After 24 months of GLM treatment, the mean Disease Activity Score using 28 joint counts with the erythrocyte sedimentation rate (DAS28-ESR) decreased from 6.7 to 3.1 ($p < 0.001$). Up to 58.9% of patients achieved a good EULAR response at 24 months. Multivariate logistic regression analysis revealed that after adjustment for other variables, a higher baseline C-reactive protein was an independent negative predictor of good EULAR responses (odds ratio, 0.82; 95% confidence interval [CI], 0.67-0.99; $p = 0.043$). During the mean follow-up period of 38.3 months, 15 (13.9%) patients discontinued GLM due to treatment failure. In multivariate analysis, high baseline ESR level, high DAS28-ESR, and the experience of biologic therapy were independent risk factors for GLM discontinuation (adjusted hazard ratio [HR], 1.03; 95% CI, 1.01-1.05; $p = 0.003$; adjusted HR, 2.93; 95% CI, 1.42-6.08; $p = 0.004$; and adjusted HR, 5.00; 95% CI, 1.75-14.26; $p = 0.003$, respectively). In receiver operator characteristic curve analysis, the optimal cutoff values of baseline ESR and DAS28-ESR for predicting drug survival were 52 mm/h (sensitivity: 60.0% and specificity: 77.4%) and 7.7 (sensitivity: 46.7% and specificity: 94.3%), respectively. During the follow-up period, 22 patients (20.4%) developed adverse events. The safety profile of GLM in this study was comparable with that in previous clinical trials.

Conclusion: GLM was effective and safe for the real-life management of Taiwanese RA patients and showed a high retention rate in biologic-naive patients compared with biologic-experienced patients.

Keywords: Efficacy; Golimumab; Real-world data; Safety; Tumor necrosis factor

1. INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease that involves the synovial tissue and causes pain, swelling, and even damage to joints. Immunosuppressants, such as conventional synthetic disease–modifying anti-rheumatic drugs (csDMARDs) and glucocorticoids, are used to inhibit inflammation and prevent further structural destruction/dysfunction. For more than 2 decades, biologic DMARDs (bDMARDs) have been used for RA treatment-refractory to csDMARDs, with the tumor necrosis factor-α (TNF-α) inhibitor (TNFi) being commonly used as first-line therapy based on the current recommendations of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) for RA management.[1,2] Although TNFi's share the same targeting cytokine, they still exhibit different features due to the drug design and manufacturing processes.

Golimumab (GLM), a monoclonal antibody targeting TNF-α, was derived from a hybridoma clone produced by transgenic mice immunized with human TNF-α, which has low immunogenicity.[3] Large randomized clinical trials (RCTs) have revealed that GLM exerts a long-term effect and is safe for patients with RA.[4] Although an RCT is mainly used to evaluate the efficacy and safety of therapy, which could be referred for the actual treatment, its results cannot be generalized because of the strict inclusion/exclusion criteria of the study design for ensuring internal validity. By contrast, real-world effectiveness of therapies reflects genuine treatment outcomes in a relatively heterogeneous population; therefore, the translation of results from clinical trials to daily practice becomes easier and influential in medical decision making.[5] However, real-world efficacy could

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be diverse in different areas/countries due to different ethnicities, health care systems, and reimbursement policies. Therefore, country-specific investigation of treatment efficacy is insightful for local clinical practice.

The effectiveness and safety of GLM have been supported by some real-world data. The GO-NICE study showed reduced disease activity and improved remission in German RA patients receiving GLM for >2 years,[6] whereas the GO-PRACTICE study revealed that GLM persistence in real life is satisfactory at 2 years and is accompanied by clinical improvements in RA in France.[7] Furthermore, a recent study indicated the real-world safety and effectiveness of GLM in Japanese RA patients, which is consistent with the positive effect of GLM in clinical trials.[8]

Due to the scarcity of studies investigating the real-life outcomes of GLM therapy in RA patients in Asia, we conducted the present investigation to characterize the real-world use, effectiveness, and safety of GLM in patients with RA. Furthermore, we analyzed drug persistence in these GLM-treated RA patients, which commonly reflects treatment satisfaction and safety. Potential predictors of low disease activity/remission or a good EULAR response and of GLM discontinuation were identified at 24 months of treatment.

2. METHODS

2.1. Patients

In the present retrospective study, we enrolled 135 patients with RA who received GLM treatment at the Allergy, Immunology and Rheumatology Division of Taipei Veterans General Hospital and Taoyuan General Hospital affiliated to the Ministry of Health & Welfare, Taiwan, from January 2014 to June 2019 (Supplementary Fig. 1, http://links.lww.com/JCMA/A118). Among them, 27 patients were excluded due to a lack of regular follow-up. All patients fulfilled the ACR 1987 revised criteria[9] or the ACR/EULAR 2010 criteria for RA classification[10] and had failed standard csDMARDs more than 6 months prior. These patients received a monthly subcutaneous injection of 50 mg GLM, which was reimbursed by the National Health Insurance Agency, Ministry of Health and Welfare (NHIA, MOHW) in Taiwan. The NHIA reimbursement criteria include high disease activity, which was defined as a disease activity score using 28 joint counts with the erythrocyte sedimentation rate (DAS28-ESR) of >5.1, and treatment failure for at least two csDMARDs, including methotrexate (MTX) (15 mg/wk), for 6 months. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and Taoyuan General Hospital, MOHW, Taiwan.

2.2. Clinical and laboratory assessments

General characteristics and clinical parameters, including 28 tender joint count (TJC), 28 swollen joint count (SJC), and DAS28-ESR,[11] were obtained at baseline and at 6, 12, 18, and 24 months after GLM initiation. Moreover, inadequate responses to previous bDMARDs, such as TNFi's (other than GLM), anti-interleukin (IL)-6 agents (tocilizumab), and Cytotoxic T-lymphocyte antigen 4 -Ig fusion protein (abatacept), and the reasons for switching to GLM were recorded. Furthermore, the dosage of concomitant csDMARDs and glucocorticoid use were recorded. Additionally, the data of laboratory tests, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide antibody (ACPA), were acquired. Charlson comorbidity index was used to assess comorbidity.[12]

2.3. Definition of clinical remission and response

Disease activity measures according to DAS28-ESR were classified into clinical remission (DAS28-ESR ≤ 2.6), low disease activity (2.6 < DAS28-ESR ≤ 3.2), moderate disease activity (3.2 < DAS28-ESR ≤ 5.1), and high disease activity (DAS28-ESR > 5.1).[13] The clinical response of GLM therapy was assessed using the EULAR response criteria, which classified patients into nonresponders, moderate responders (DAS28-ESR ≤ 3.2 plus a decrease >0.6 and ≤1.2, or a 3.2 < DAS28-ESR ≤ 5.1 and a decrease >0.6, or a DAS28-ESR > 5.1 and a decrease >1.2), or good responders (DAS28 ≤ 3.2 with a decrease in DAS28 > 1.2).[14] Disease activity measures and EULAR responses were evaluated at 6, 12, 18, and 24 months after GLM therapy initiation. Primary failure was defined as a lack of improvement in clinical signs and symptoms 12 to 16 weeks after GLM initiation. Secondary failure was defined as an initial clinical response after receiving GLM followed by the loss of its efficacy.[15]

2.4. Safety issues

The safety profile was determined during the follow-up period that included infusion reactions, infections such as pneumonia or herpes zoster, malignancies, cardiovascular events, and death. Furthermore, flares of hepatitis B infection or tuberculosis after GLM initiation were recorded.

2.5. Statistical analysis

Baseline characteristics were compared using the *chi*-squared test or Fisher's exact test for categorical variables. An independent Student's *t* test was performed to compare numerical data with a normal distribution, and the Mann–Whitney *U* test was used for analyzing nonparametric data. Changes in DAS28-ESR, ESR, TJC, and SJC were compared with the corresponding values at baseline by using the paired sample *t* test. The factors associated with a favorable EULAR response or GLM discontinuation were identified using the Cox proportional hazard model. All covariates were included in a multivariable model with automatic backward elimination. Receiver operator characteristic (ROC) analysis was conducted, and the area under the curve (AUC) was calculated to measure prediction accuracy. The cumulative risk of GLM discontinuation was estimated using the Kaplan–Meier method, and statistical differences were examined using the log-rank test. Only patients with treatment failure and drug intolerance were included in the analysis of discontinuation. Missing data were replaced using the last-observation-carried-forward technique. A p-value of <0.05 was considered significant. Data were analyzed using Statistical Package for Social Sciences (SPSS) software, version 26.0 (IBM SPSS Statistics for Windows, IBM, Armonk, New York, USA).

3. RESULTS

3.1. Demographic and clinical characteristics of patients

In total, 108 patients were evaluated in this study after excluding patients who were not regular with follow-up (Table 1). Of them, 95 patients (88%) were female, and the median disease duration was 4.0 years. The mean age at bDMARD initiation was 59.2 years. The mean DAS28-ESR and ESR at the baseline were 6.7 and 42.7 mm/h, respectively, whereas the median baseline CRP level was 0.8 mg/dL. In the study population, 58 (75.3%) patients had positive results on ACPA, and 89 (82.4%) patients had RF.

In this study, 27 patients (25.0%) had received other bDMARDs previously, and 104 patients (96.3%) used concomitant csDMARDs, including MTX, leflunomide, sulfasalazine, and/or hydroxychloroquine, during the 24-month period of GLM treatment. Sixty-three (58.3%) patients received MTX at a mean dosage of 9.1 mg/wk.

Table 1

Demographics and characteristics of patients undergoing golimumab treatment and characteristics based on EULAR response at 24 months

Characteristics	Total	EULAR Response at 24 mo		p
		Moderate	Good	
Patient number	108	35 (41.2)	50 (58.8)	—
Female	95 (88.0)	31 (88.6)	47 (94.0)	0.439
Age at diagnosis of RA (y)	53.2 ± 13.2	52.0 ± 12.9	53.3 ± 13.5	0.668
Age at biologics initiation (y)	59.2 ± 13.3	58.7 ± 11.7	58.3 ± 13.8	0.872
Disease duration (y)	4 (1, 9)	4 (1, 11)	3.5 (2, 8)	0.201
Baseline TJC	16.0 ± 5.4	15.8 ± 5.9	15.9 ± 5.1	0.887
Baseline SJC	10.4 ± 4.2	10.6 ± 3.9	10.5 ± 4.7	0.943
Baseline ESR (mm/h)	42.7 ± 23.7	44.3 ± 22.8	39.0 ± 21.5	0.275
Baseline CRP (mg/dL)	0.8 (0.2-2.5)	1.2 (0.4-3.6)	0.4 (0.1-1.6)	0.046*
Baseline DAS28-ESR	6.7 ± 0.8	6.7 ± 0.8	6.6 ± 0.8	0.671
RF positive	89 (82.4)	26 (74.3)	43 (86.0)	0.259
Anti-CCP antibody positive	58/77 (75.3)	18/23 (78.3)	23/35 (65.7)	0.384
Charlson's comorbidity index	1 (1, 2)	1 (1, 1)	1 (1, 1.3)	0.591
Prior bDMARD therapy	27 (25.0)	8 (22.9)	10 (20.0)	0.792
Concomitant medications				
csDMARDs	104 (96.3)	35 (100.0)	48 (96.0)	0.510
MTX use	63 (58.3)	23 (65.7)	27 (54.0)	0.371
MTX dosage (mg/wk) (n = 63)	9.1 ± 3.8	9.5 ± 3.8	9.0 ± 4.2	0.677
Glucocorticoid use	39 (36.1)	10 (28.6)	15 (30.0)	1.000
GLM duration (mo)	38.3 ± 18.6	41.1 ± 15.0	47.3 ± 15.0	0.063

Data are presented as frequency (percentage), mean ± SD, or median (interquartile range).

Anti-CCP = anti-cyclic citrullinated peptide; bDMARD = biologic disease-modifying antirheumatic drug; CRP, = C-reactive protein; csDMARD = conventional synthetic DMARD; DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; GLM = golimumab; MTX = methotrexate; RA = rheumatoid arthritis; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.

*$p < 0.05$.

3.2. Disease activity improvement with GLM

After 24 months of GLM treatment, the mean ESR decreased from 42.7 ± 23.7 mm/h at baseline to 20.1 ± 15.3 mm/h ($p < 0.001$; Fig. 1A). Furthermore, the mean DAS28-ESR at 24 months significantly improved compared with that at baseline (from 6.7 ± 0.8 to 3.1 ± 0.7, $p < 0.001$; Fig. 1B). Moreover, the means of TJC and SJC reduced after 24 months of GLM treatment (both $p < 0.001$; Fig. 1C, D). The percentages of patients who achieved low disease activity or remission according to DAS28-ESR criteria increased significantly at 6, 12, 18, and 24 months after GLM initiation, which were 23.8%, 45.6%, 55%, and 58.9%, respectively (Fig. 1E). Good EULAR responses at 6, 12, 18, and 24 months were achieved by 22.9%, 44.7%, 53.8%, and 58.8% of patients, respectively (Fig. 1F).

3.3. Predictors of good EULAR responses at 24 months

In this study, 85 patients completed 24 months of follow-up. Of these, 50 (58.8%) achieved good EULAR responses, 35 (41.2%) achieved moderate EULAR responses, and none had a poor EULAR response (Table 1). Compared with patients having good EULAR responses, those having moderate EULAR responses had higher CRP levels ($p = 0.046$) at baseline. No significant differences were noted in age at diagnosis, age at GLM initiation, sex, DAS28-ESR, TJC, SJC, ESR, RF, ACPA, CCI, prior bDMARD therapy, concomitant MTX, and glucocorticoid use.

Predictors of a good EULAR response to GLM therapy were identified using univariate logistic regression, and a high baseline CRP level was associated with a reduced likelihood of achieving a good EULAR response at 24 months (odds ratio [OR], 0.83; 95% confidence interval [CI], 0.68-1.01), although nonsignificant ($p = 0.056$; Table 2). The findings of multivariate logistic regression with adjustment for other variables revealed that a high baseline CRP level was associated with a low likelihood of achieving a good EULAR response at 24 months (OR, 0.82; 95% CI, 0.67-0.99; $p = 0.043$).

3.4. Drug survival and retention rate

The mean duration of GLM treatment was 38.3 months, and 87 (80.6%) patients continued treatment during the follow-up period. Moreover, 15 patients discontinued GLM due to poor effectiveness; 1 (0.9%) patient had primary failure, which indicates no clinical improvement after GLM initiation for 12 weeks, and 14 (13%) patients had secondary failure, which indicates clinical improvement initially but treatment failure after a certain period. As shown in Fig. 2A, the retention rates of GLM were 92.6%, 84.8%, and 76.8% after 12-, 24-, and 70-month treatment, respectively.

The baseline ESR and DAS28-ESR in the GLM discontinuation group were significantly higher than those in the GLM persistence group (56.5 ± 30.7 vs 40.5 ± 21.7 mm/h, $p = 0.015$ and 7.2 ± 0.9 vs 6.7 ± 0.8, $p = 0.022$, respectively; Table 3). In addition, compared with the GLM persistence group, more patients in the GLM discontinuation group had concomitant glucocorticoid use during GLM therapy period (60.0% vs 32.3%, $p = 0.047$).

3.5. Factors associated with drug retention in RA patients receiving GLM

We analyzed factors associated with drug retention in RA patients undergoing GLM by using the Cox proportional hazard model. In univariate analysis, high baseline ESR, higher DAS28-ESR, prior bDMARD therapy before GLM, and glucocorticoid use were related to poor GLM drug retention (all $p < 0.005$; Table 4). In the multivariate logistic regression model, high baseline ESR and higher DAS28-ESR were independent risk factors

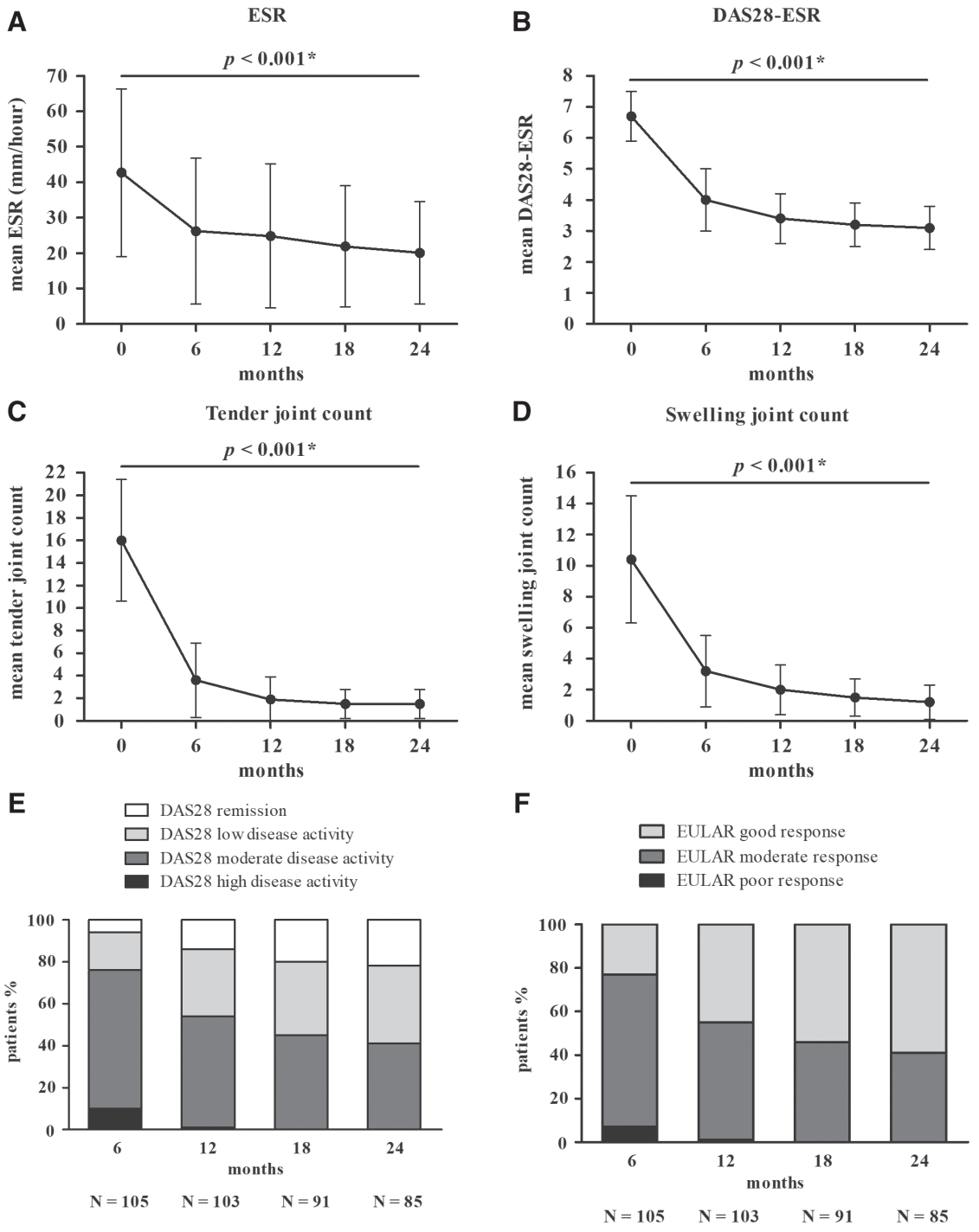

Fig. 1 Effect of treatment with golimumab on disease parameters and clinical remission status of patients with RA over time. A, Mean erythrocyte sedimentation rate (ESR). B, Mean Disease Activity Score-28 with ESR (DAS28-ESR). C, Mean tender joint count. D, Mean swelling joint count. E, Patient categorical distribution of disease activity based on the DAS28-ESR score. F, Distribution of the EULAR response achievement rate. Error bars show SD. *The *p*-value <0.001 compared with baseline. EULAR = European League Against Rheumatism; RA = rheumatoid arthritis.

for GLM discontinuation after adjustment for other related factors (adjusted hazard ratios [HRs], 1.03; 95% CI, 1.01-1.05; p = 0.003 and adjusted HR, 2.93; 95% CI, 1.42-6.08; p = 0.004, respectively). In addition, prior bDMARD therapy was another independent risk factor for GLM discontinuation (HR after adjustment for baseline ESR and CRP levels, 3.26; 95% CI, 1.14-9.31; p = 0.027 and HR after adjustment for baseline DAS28-ESR and CRP levels, 5.00; 95% CI, 1.75-14.26; p = 0.003, respectively; Fig. 2B).

To determine the optimal cutoff level of baseline ESR and DAS28-ESR to predict GLM discontinuation in our cohort, ROC analysis was used. The corresponding AUC of the ROC curve of baseline ESR was 0.685 (95% CI, 0.528-0.842, p=0.022), and the optimal cutoff value of 52 mm/h was determined

Table 2

Factors associated with EULAR good response at 24 months

	Univariate Analysis		Multivariable Analysis[a]		Multivariable Analysis[b]	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Female	2.02 (0.42-9.66)	0.378				
Age at diagnosis of RA (y)	1.01 (0.98-1.04)	0.664				
Age at biologics initiation (y)	1.00 (0.96-1.03)	0.870				
Disease duration (y)	0.96 (0.89-1.03)	0.205				
Baseline ESR (mm/h)	0.99 (0.97-1.01)	0.275				
Baseline CRP (mg/dL)	0.83 (0.68-1.01)	0.056	0.82 (0.67-0.99)	0.043*	0.82 (0.67-0.99)	0.043*
Baseline DAS28-ESR	0.89 (0.52-1.53)	0.667				
RF positive	2.13 (0.71-6.40)	0.179				
Anti-CCP antibody positive (n= 77)	0.53 (0.16-1.79)	0.308				
Charlson's comorbidity index	1.16 (0.68-1.97)	0.591				
Prior bDMARD therapy	0.84 (0.30-2.41)	0.751				
MTX use	0.61 (0.25-1.50)	0.282	0.55 (0.22-1.38)	0.202	0.55 (0.22-1.38)	0.202
Glucocorticoid use	1.07 (0.41-2.77)	0.887				

Baseline ESR and baseline DAS28-ESR were introduced into the multivariable model separately due to the collinearity between these two parameters.

*$p < 0.05$.

Anti-CCP = anti-cyclic citrullinated peptide; bDMARD = biologic disease-modifying antirheumatic drug; CI = confidence interval; CRP = C-reactive protein; csDMARD = conventional synthetic DMARD; DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; MTX = methotrexate; NA = not available; OR = odds ratio; RA = rheumatoid arthritis; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.

[a]Did not include DAS28-ESR.

[b]Did not include baseline ESR.

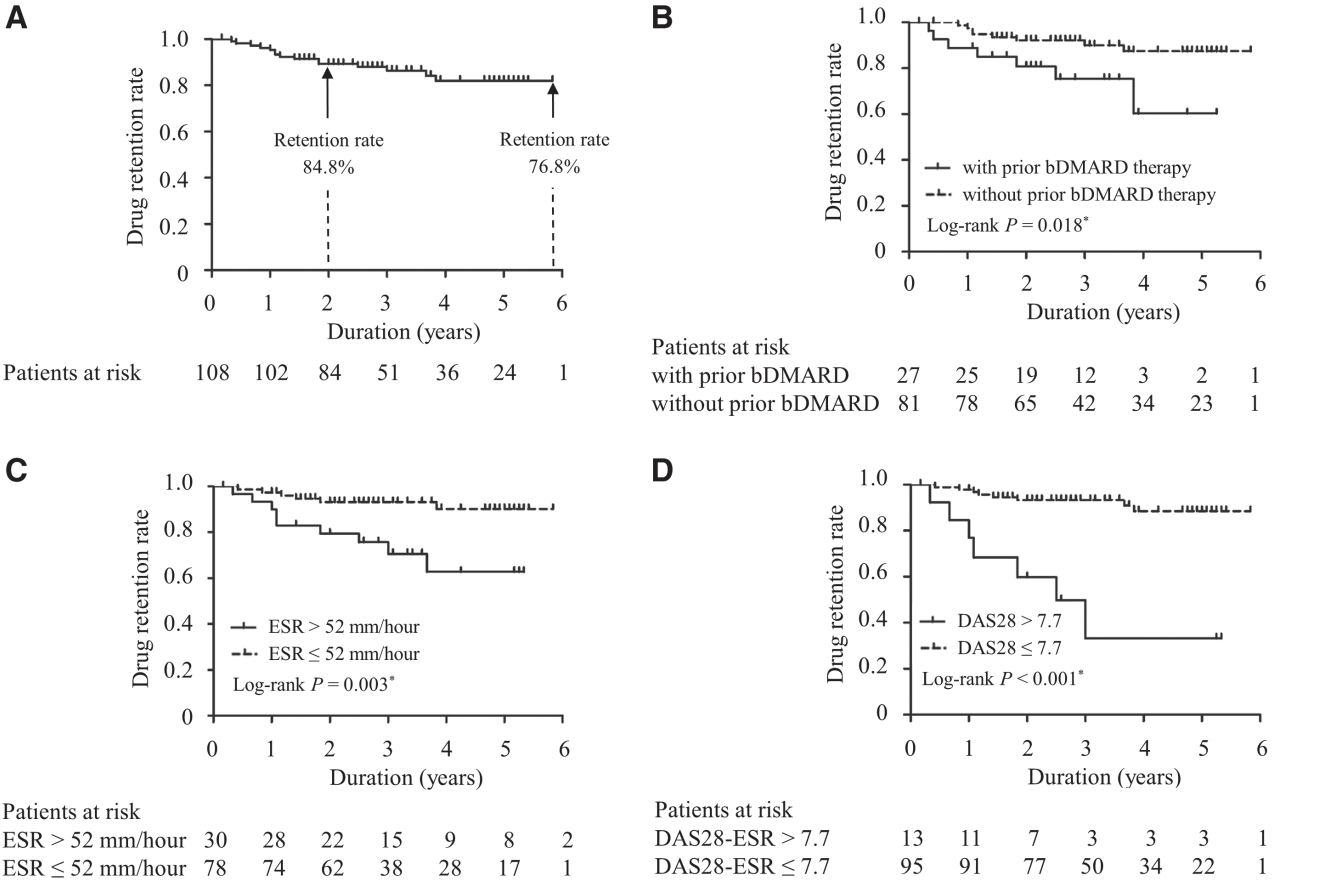

Fig. 2 Drug retention rate over 70 mo of golimumab treatment in all 108 patients (A), stratified by with or without prior biological disease-modifying anti-rheumatic drug (bDMARD) therapy (B), stratified by baseline ESR > or ≤ 52 mm/h (C), and stratified by baseline DAS28-ESR >7.7 or ≤7.7 (D). The analysis of golimumab discontinuation only evaluated patients with treatment failure and drug intolerance. The incidence of golimumab discontinuation was evaluated by the Kaplan–Meier analysis and Log-rank test.

Table 3

Characteristics of RA patients continuing and discontinuing golimumab due to poor treatment response during the follow-up (n = 108)

Characteristics	Continued GLM	Discontinued GLM	*p*
Patient number	93	15	-
Female	82 (88.2)	13 (86.7)	1.000
Age at diagnosis of RA (y)	53.4 ± 13.6	52.7 ± 11.0	0.853
Age at biologics initiation (y)	59.0 ± 13.8	60.0 ± 10.4	0.798
Disease duration (y)	5.7 ± 6.3	7.4 ± 6.2	0.345
Baseline TJC	15.8 ± 5.4	17.9 ± 4.8	0.147
Baseline SJC	10.4 ± 4.2	10.8 ± 3.9	0.741
Baseline ESR (mm/h)	40.5 ± 21.7	56.5 ± 30.7	0.015*
Baseline CRP (mg/dL)	0.7 (0.2, 2.5)	0.8 (0.3, 2.8)	0.890
Baseline DAS28-ESR	6.7 ± 0.8	7.2 ± 0.9	0.022*
RF positive	78 (83.9)	11 (73.3)	0.297
Anti-CCP antibody positive (n = 77)	47 (72.3)	11 (91.7)	0.274
Charlson's comorbidity index	1 (1, 1.5)	1 (1, 2)	0.074
Prior bDMARD therapy	20 (21.5)	7 (46.7)	0.053
Concomitant medications			
csDMARDs	90 (96.8)	14 (93.3)	0.455
MTX	56 (60.2)	7 (46.7)	0.401
MTX dosage (mg/wk) (n = 63)	9.1 ± 3.9	8.6 ± 3.2	0.730
Glucocorticoid use	30 (32.3)	9 (60.0)	0.047*

Anti-CCP = anti-cyclic citrullinated peptide; bDMARD = biologic disease-modifying antirheumatic drug; CRP = C-reactive protein; csDMARD = conventional synthetic DMARD; DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate; GLM = golimumab; MTX = methotrexate; RA = rheumatoid arthritis; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count; Data are presented as frequency (percentage), mean ± SD, or median (interquartile range).
*$p < 0.05$.

(sensitivity: 60.0% and specificity: 77.4 %), while the corresponding AUC of the ROC curve of DAS28-ESR was 0.698 (95% CI, 0.538-0.858, $p = 0.015$), and the optimal cutoff value was 7.7 (sensitivity: 46.7% and specificity: 94.3%; Supplementary Fig. 2, http://links.lww.com/JCMA/A118). The cumulative survival rate decreased in the group of patients who had high levels of inflammatory markers (ESR > 52 mm/h) and high disease activity (DAS28-ESR > 7.7) (Fig. 2C, D).

3.6. Safety

In this study, the total GLM exposure duration was 343 patient years. During the follow-up period, 22 patients (20.4%) developed adverse events after receiving at least one dose of GLM. Only two patients (1.9%) experienced allergic reactions to GLM exposure. Ten patients (9.3%) developed serious infection, and the incidence rate (IR; 95% CI) was 2.90 (0.04-0.15) per 100 patient-years. The most frequent serious infection was pneumonia (n = 5, 4.6%), followed by cellulitis (n = 3, 2.8%), urinary tract infection (n = 1, 0.9%), and perianal abscess (n = 1, 0.9%). In addition, nine (8.3%) patients developed herpes zoster, and the overall IR (95% CI) was 2.6 (0.03-0.14) per 100 person-years. Eighty-five patients underwent routine screening for latent tuberculosis (LTB) infection through the interferon-gamma release assay, and nine (10.6%) tested positive. All of them received treatment for LTB infection with isoniazid, and none developed tuberculosis disease. Five were hepatitis B virus (HBV) carriers (hepatitis B surface antigen-positive). None of them received antiviral prophylaxis, and none had HBV reactivation. Two patients (1.9%) were newly diagnosed with cancer during GLM therapy; one had cholangiocarcinoma, and the other had renal cell carcinoma. The IR (95% CI) of new malignancies was 0.6 (–0.01 to 0.04) per 100 person-years for patients receiving GLM. The most common adverse events leading to GLM discontinuation were pneumonia (n = 3, 2.8%) and cancer (n = 2, 1.9%). Two patients (1.9%) died, and the IR (95% CI) for all-cause mortality was 0.6 (–0.01 to 0.04) per 100 person-years; both of them died due to pneumonia; one patient died after 9 months of GLM treatment, and the other patient died after 2 years of GLM treatment.

4. DISCUSSION

This is the first study to investigate the real-world efficacy, safety, and drug persistence of GLM and associated risk factors in a

Table 4

Factors associated with the risk of golimumab discontinuation (n = 108)

Variable	Univariate Analysis HR (95% CI)	*p*	Multivariable Analysis[a] HR (95% CI)	*p*	Multivariable Analysis[b] HR (95% CI)	*p*
Female	0.60 (0.13-2.65)	0.496				
Age at diagnosis of RA (y)	1.00 (0.96-1.04)	0.899				
Age at biologics initiation (y)	1.01 (0.97-1.05)	0.651				
Disease duration (y)	1.02 (0.95-1.10)	0.507				
Baseline ESR (mm/h)	1.02 (1.003-1.04)	0.018	1.03 (1.01-1.05)	0.003*		
Baseline DAS28-ESR	2.32 (1.07-5.04)	0.034			2.93 (1.42-6.08)	0.004*
Baseline CRP (mg/dL)	0.95 (0.73-1.22)	0.667	0.78 (0.58-1.04)	0.090	0.84 (0.63-1.10)	0.204
RF positive	0.63 (0.20-2.00)	0.437				
Anti-CCP antibody positive (n = 77)	3.88 (0.50-30.11)	0.194				
Charlson's comorbidity index	1.39 (0.99-1.95)	0.058				
Prior bDMARD therapy	3.23 (1.16-8.99)	0.025	3.26 (1.14-9.31)	0.027*	5.00 (1.75-14.26)	0.003*
csDMARDs	0.33 (0.04-2.59)	0.291				
MTX	0.64 (0.23-1.76)	0.387				
Glucocorticoid use	2.94 (1.05-8.26)	0.041				

Baseline ESR and baseline DAS28-ESR were introduced into the multivariable model separately due to the collinearity between these two parameters.
*$p < 0.05$.
Anti-CCP = anti-cyclic citrullinated peptide; bDMARD = biologic disease-modifying antirheumatic drug; CI = confidence interval; CRP = C-reactive protein; csDMARD = conventional synthetic DMARD; DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate; MTX = methotrexate; NA = not available; HR = hazard ratio; RA = rheumatoid arthritis; RF = rheumatoid factor; SJC = swollen joint count; TJC = tender joint count.
[a]Did not include DAS28-ESR.
[b]Did not include baseline ESR.

Taiwanese RA cohort. We demonstrated that GLM offers long-term efficacy and safety up to 2 years in patients with established RA. Furthermore, GLM has a high drug retention rate in real-life settings, particularly in first-line bDMARD therapy. Moreover, baseline ESR and DAS28-ESR predict high drug persistence rates, which might provide insights into the use of these factors in the prediction of long-term disease control.

Few real-world reports are available on the DAS28-ESR remission rate among patients with RA after receiving GLM. The current study revealed that the 2-year DAS28-ESR remission rate with GLM use was approximately 24%. This was less than that reported in the real-world GO-NICE study in Germany (44.6%, 82 of 184), which may be due to the higher baseline DAS28-ESR (6.7 vs 5) and ESR levels (42.7 vs 28.4 mm/h) in our study than in this study.[6] However, we still demonstrated that the percentages of patients who achieved remission or low disease activity according to the DAS28-ESR criteria increased from 23.8% at 6 months to 58.9% at 24 months after GLM initiation. This indicates that more than half of the patients with RA had satisfactory disease control after GLM treatment for 2 years in this cohort.

Approximately 23% of our patients achieved good EULAR responses at 6 months after GLM initiation. We presented the efficacy of GLM in RA as shown in other reports. Consistently, 24.4% of patients with RA achieved EULAR response under GLM treatment in a recent Japanese postmarketing surveillance (PMS) study.[16] In the GO-MORE study, which evaluated the efficacy and safety of GLM as add-on therapy in patients with RA with DMARD treatment, up to 35.98% of GLM-treated patients with RA had EULAR response.[17] Several differences across these studies may explain the higher EULAR response in the GO-MORE study than in our study. The GO-MORE study predominantly enrolled Caucasians (69.6%); this may have affected treatment effectiveness. Inflammation burden at baseline, such as the ESR, was lower in the GO-MORE study (34.9 mm/h) than in our cohort (42.7 mm/h) and in the Japanese PMS study (48.37 mm/h). Furthermore, the mean DAS28-ESR was lower in the GO-MORE study than in our study (5.97 vs 6.7). Moreover, the present investigation and the Japanese PMS study were conducted in real-world settings, whereas the GO-MORE study was an open-label RCT with a less heterogeneous patient population; these differences may have led to a higher response rate. Furthermore, we continued to measure the EULAR response for up to 2 years. Importantly, up to 59% of patients achieved good EULAR responses after 2 years of GLM therapy. Increases in the response rate indicated that continuous GLM treatment not only maintained efficacy but also constantly improved disease activity. Notably, this is the first study to demonstrate long-term efficacy in terms of good EULAR responses in GLM-treated RA patients.

Persistence in therapy is highly relevant in disease management, particularly for chronic rheumatic diseases, as it can affect patient outcomes, reduce health care use, and avoid treatment switching.[18] The drug persistence for GLM is generally similar to that for other TNFi in patients with RA in real-world studies,[19] which can be attributed to the convenient dosing frequency, satisfactory injection site reaction,[20] and low reported GLM immunogenicity.[21] Therefore, to better understand the performance of GLM in Taiwan, we investigated the persistence rate of GLM during the follow-up period. Overall, 80% of patients remaining on GLM after 2 years if considering drop-out for any reason as discontinuation. Considering discontinuation due to primary or secondary failure, there are approximately 85% of patients continued GLM treatment after 2 years. A recent study from Taichung Veterans General Hospital revealed that the persistence rate of TNFi was generally higher than that of other biologics with a different action mechanism.[22] Although the reported data were not further stratified based on the TNFi type, the persistence rate of GLM in our study was similar to that of the overall TNFi group in that cohort. Furthermore, the persistence rate of GLM was higher in this study than in other real-world reports from other countries. For example, a French study concluded that the 2-year drug persistence was approximately 57% in RA patients,[7] while it was close to 60% according to the Spanish BIOBADASER registry.[23] The 2-year persistence rate of GLM in an Italian real-world study was also around 64%.[24] In addition, the GLM persistence rate decreased rapidly with the follow-up time in those studies, whereas it declined by less than 10% from a 2- to 5-year follow-up period in the current investigation; up to 77.0% of our patients continued GLM treatment for more than 5 years. We investigated potential contributors to the high persistence of GLM among patients with RA in Taiwan compared with that in other countries. First, different ethnicities, geographic areas, and data sources may result in varied persistence rates between studies. Second, bDMARD treatment in combination with MTX is a common strategy in Taiwan, which was previously shown to be associated with higher persistence than with bDMARD monotherapy.[25] Lastly, an official reimbursement-based health care system is well-established in Taiwan, which contributes to less economic burden for RA patients when using costly biologics.

Factors affecting drug survival in GLM-treated RA patients were identified to be prior biologic therapy and high baseline DAS28-ESR. Previous studies have shown similar results regarding the effect of prior bDMARD therapy on drug discontinuation.[26–28] For instance, data from the Italian GISEA registry revealed that the GLM persistence rate among first-line biologic inadequate responders (bDMARD-IR) was 11.7% lower than that in bDMARD-naive patients in 2 years (73.1% vs 61.4%), which is consistent with our observation.[27] Furthermore, we demonstrated that only patients with baseline DAS28-ESR >7.7 had a high risk of GLM treatment discontinuation due to the lack of efficacy, indicating that high disease activity at baseline predicted poor drug retention. Nevertheless, only 12% of patients had extremely high disease activity at baseline, indicating that GLM was continued and clinically effective among the majority of the RA patients in this cohort study. The safety profile of GLM in the current study was generally consistent with that in previous clinical trials.[29] The observed number of deaths was less than expected in an age- and sex-adjusted population. The observed serious infection rate (2.9 per 100 patient-years) was slightly lower than in the 5-year result (3.29 per 100 patient-years) in five phase III trials.[30] None of the patients with LTB infection and HBV carriers encountered the reactivation of TB and HBV, respectively, reflecting a favorable outcome of the well-executed risk management plan in monitoring TB and HBV before and during TNFi treatments in Taiwan.

Although our results demonstrated that GLM was efficacious and well-tolerated among RA patients, this investigation had some limitations. One is the small sample size, which may not be heterogeneous and representative of the overall RA population in Taiwan. Multicenter clinical research can offer better quality results than single-center studies. However, multicenter studies are considerably more complex, and sampling bias may occur. In this study, all enrolled patients fulfilled the same criteria for RA classification and received similar treatment regimens according to the reimbursement criteria of Taiwan's National Health Insurance guidelines. The therapeutic options of RA, including csDMARDs and bDMARDs, were available in both medical centers. However, some bias may exist in laboratory results due to differences in laboratory settings between the two medical centers. Nevertheless, our findings revealed the predictors of GLM discontinuation, which can be considered by clinical rheumatologists during treatment decisions and considering treatment options for oriental patients with RA.

In conclusion, the study findings confirm the real-world effectiveness, safety, and GLM persistence in active RA patients in Taiwan, a part of Asia–Pacific. Moreover, this study provided insights into GLM discontinuation predictors, such as prior biologic therapy and extremely high baseline DAS28-ESR, in the long-term observational time frame.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A118.

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