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ORIGINAL RESEARCH

A Real-World Claims Database Study Assessing Long-Term Persistence with Golimumab Treatment in Patients with Rheumatoid Arthritis in Japan

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ABSTRACT

Introduction: The persistence of golimumab (GLM) treatment in Japanese patients with rheumatoid arthritis (RA) has been evaluated previously, but evidence of long-term real-world use is lacking. This study assessed the long-term persistence of GLM use, its influencing factors, and impact of prior medications in patients with RA in actual clinical practice in Japan.

Methods: This is a retrospective cohort study of patients with RA using data from a hospital insurance claims database in Japan. The identified patients were stratified as only GLM treatment (naïve), had one biological disease-modifying anti-rheumatic drug (bDMARD)/Janus kinase (JAK) inhibitor treatment prior to GLM [switch (1)] and had at least two bDMARDs/JAK prior to GLM treatment [switch (≥ 2)]. Patient characteristics were evaluated using descriptive statistics. Kaplan–Meier survival and Cox regression methods were used to analyze GLM persistence at 1, 3, 5, and 7 years and the associated factors. Treatment differences were compared using a log-rank test.

Results: GLM persistence rate in the naïve group was 58.8%, 32.1%, 21.4%, and 11.4% at 1, 3, 5, and 7 years, respectively. Overall persistence rates in the naïve group were higher than in switch groups. Higher GLM persistence was observed among patients aged 61–75 years and those concomitantly using methotrexate (MTX). Also, women were less likely to discontinue treatment compared to men. Higher Charlson Comorbidity Index score, initial GLM dose of 100 mg, and switch from bDMARDs/JAK inhibitor were related to a lower persistence rate. As a prior medication, infliximab showed the longest persistence for subsequent GLM, and using this as a reference, tocilizumab, sarilumab, and tofacitinib subgroups had significantly shorter persistence, respectively (p = 0.001, 0.025, 0.041).

Conclusion: This study presents the long-term real-world results for persistence of GLM and its potential determinants. These most recent and long-term observations demonstrated that GLM

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and other bDMARDs continue to benefit patients with RA in Japan.

Keywords: Biologics; Golimumab; Persistence; Real-world database; Rheumatoid arthritis

Key Summary Points

Why carry out this study?

Long-term treatment with golimumab (GLM) and other biological disease-modifying anti-rheumatic drugs (bDMARDs) over the past 7 years has not yet been reviewed in day-to-day clinical practice.

There is insufficient evidence on patient characteristics associated with long-term use of GLM after switching from bDMARDs/Janus kinase (JAK) inhibitor treatments in Japan.

There is an ambiguity about which bDMARDs/JAK inhibitor prior to GLM treatment could have a potential impact on the persistence of GLM.

What was learned from the study?

The persistence of GLM in patients with RA was relatively higher than other bDMARDs and JAK inhibitor treatments throughout the 7-year observation period.

Patients who received multiple bDMARDs prior to GLM treatment had a lower persistence rate.

Patients being female, naïve to GLM treatment, and receiving concomitant methotrexate were associated with longer persistence of GLM. These findings will be helpful to healthcare providers in developing effective treatment strategies in the future.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily starts with symmetric synovitis and may lead to progressive joint-related disabilities [1]. An inadequately diagnosed or treated joint destruction progresses and causes irreversible physical dysfunction, resulting in permanent disabilities that affect patients' quality of life and subsequently contribute to an increased socioeconomic burden [2]. The estimated prevalence of RA in Japan is 825,000, which equates to nearly 0.65% of the Japanese population [3]. Current treatments for RA include traditionally used non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids as well as conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) including methotrexate, sulfasalazine, bucillamine, tacrolimus, and iguratimod. Furthermore, Janus kinase (JAK) inhibitors, as well as biological disease-modifying anti-rheumatic drugs (bDMARDs) such as tumor necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) inhibitors, IL-1 inhibitors, B cell and T cell co-stimulation inhibitors, have recently been approved (Supplementary Table S1) [3]. The introduction of bDMARDs has transformed RA treatment; apart from preventing disease progression, they have been shown to improve quality of life and reduce mortality [4–6]. Despite these benefits, complete long-term disease remission is not achieved in many patients. Clinical trial data indicates that approximately 30% of patients with RA do not respond to treatment with the first bDMARDs, and 40% of such patients fail on second bDMARD treatment, resulting in a significant number of patients receiving treatment with three or more bDMARDs [7, 8]. However, there is little evidence to support the bDMARD switching strategy [9], and a clear consensus has not been reached.

According to published reports from observational studies [10, 11], meta-analysis [12], and systematic reviews [13], patients who switched to the second or third bDMARDs after an inadequate response (IR) to the first bDMARD used had a lower probability of achieving a clinical

response. The clinical efficacy of TNF-targeting monoclonal antibody golimumab (GLM) has been demonstrated in patients with RA who had previously discontinued anti-TNF therapy because of IR, intolerance, or other reasons [8]. The post hoc analysis of post-marketing surveillance (PMS) data for GLM reports that switching to GLM caused a clinical response regardless of the number of previous bDMARDs and mechanism of action (MoA) of pretreatment bDMARDs; however, the evaluation period considered was as short as 24 weeks [14]. Furthermore, the retention rate (i.e., persistence) of bDMARDs varies considerably depending on the country and drug [15]. A systematic review of 52 global studies indicated that the retention rates of bDMARDs at 1 year ranged from 32.0% to 90.9% [16]. These large variations can be attributed to institutional and cultural factors in the region or during the evaluation period, making direct comparison of survey results for each country difficult.

This retrospective analysis of records from the Japanese Medical Data Vision (MDV) health claims database investigated the background of patients with RA and the long-term retention rate (persistence) of GLM in association with prior experience of bDMARDs/JAK inhibitor treatments in a real-world setting in Japan.

METHODS

Data Source

This retrospective cohort study was conducted using data sets extracted from the MDV health claims database for a period of 13 years, from 2008 to 2020. MDV is a hospital-based database that is recognized as one of the largest and most credible commercially available medical databases in Japan. Briefly, the MDV database contains health insurance claims, Diagnosis Procedure Combination (DPC) data, and administrative data from over 400 hospitals covering over 30 million patients. This database was chosen over other databases, as it provides data on elderly patients, making it more suitable for research of RA. It provides data on medical treatment information which includes age, gender, disease name, disease diagnoses, in- or out-patient status, drug prescriptions, dosage, blood test, medical procedures, and reimbursement costs. These data were analyzed to investigate the background of patients with RA and the long-term persistence of GLM in Japan. The extracted data are unlinkable (to any personal patient information) and were anonymized before receipt. Diagnoses of patients were coded according to the International Classification of Diseases, 10th Revision (ICD-10) coding scheme and indicated as either "confirmed" or "suspected" diagnosis. Data of only patients with a "confirmed" diagnosis of RA were used. As per the ethical guidelines for medical and health research involving humans issued by the Japanese Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science, and Technology the process of informed consent was not applicable for this study.

Study Design and Population

This study investigated the background of patients with RA and the long-term persistence of GLM in Japan after 1, 3, 5, and 7 years of the treatment. Patients were stratified into two groups: the "GLM naïve group", in which GLM was prescribed as the first bDMARD; and the "treatment switch group", in which GLM was prescribed as subsequent bDMARD. The treatment switch group was further divided into the switch (1) group and the switch ($\geq$ 2) group based on the number of times patient had switched treatment, and then further subdivided into specific subgroups (i.e., TNF inhibitors, IL-6 inhibitors, CTLA4-Ig, and JAK inhibitors) depending on the bDMARD the patient received before being administered GLM (Supplementary Table S1). Patients in switch groups were not further stratified into separate treatment subgroups and were evaluated as a whole.

For the GLM naïve group, data from patients with a confirmed RA diagnosis (excluding suspected cases) during the study period defined by ICD-10 codes M05 and M06 (Supplementary Table S2), who were aged at least 18 years on the

index date and received a prescription for GLM at least once after the index date, were analyzed. The index date was defined as the first date in the database when GLM was prescribed post first RA diagnosis date. Patients were considered as discontinued if they switched to another target treatment or if the actual refill prescription date was greater than 60 days post prescription period. The next prescription date was regarded as the discontinuation date (Fig. 1). Patients who could not be traced 3 months before and 1 year after the index date were excluded, as information from 3 months before the index date was used to collect baseline characteristics and long-term endpoint assessments required information from 1 year after the index date. Patients with RA who also had Crohn's disease, ankylosing spondylitis, juvenile arthritis, psoriasis, psoriatic arthritis, ulcerative colitis, or Behçet's disease were excluded (Supplementary Table S3). The persistence rate was defined as the time (days) from the index date (treatment initiation) till the medication discontinuation; this definition is in agreement with earlier database studies in RA or other disease areas [17–19].

For the treatment switch group, patients prescribed a JAK inhibitor or a bDMARD other than GLM during the study period who met the same inclusion and exclusion criteria as the primary endpoints were analyzed. For this group, the index date was defined as the first date in the database when bDMARDs or a JAK inhibitor was prescribed after the first RA diagnosis. Patients who received prescriptions for bDMARDs or a JAK inhibitor at least once after the index date were included.

Endpoints

This study investigated the GLM persistence rate after 1, 3, 5, and 7 years of GLM treatment in the GLM-naïve and treatment switch groups. The treatment duration (i.e., time between the index date and the GLM discontinuation date) and influence of patient demographics or treatment patterns on the persistence rate were estimated. The persistence rate in both treatment groups was further examined on the basis of demographic group categories of age, gender, concomitant use of methotrexate (MTX), Charlson Comorbidity Index (CCI) score, initial dose of GLM, and number of previous biologic therapies to assess the effect of these factors on the persistence rate.

Statistical Analysis

Descriptive statistics were used to estimate the number of patients, mean, and standard deviation for continuous variables and the frequency distribution for categorical variables. The persistence rate in each treatment group was estimated using the Kaplan–Meier method. The numbers at risk, the cumulative persistence rate and its two-sided 95% confidence interval (CI) were provided at each timepoint. The median

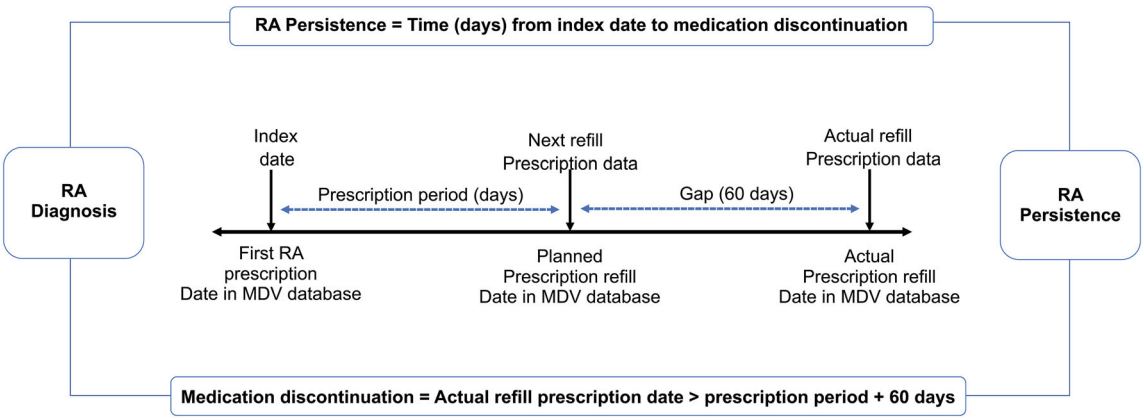


Fig. 1 Definition of persistence in base case (60 days medication gap). *MDV* Medical Data Vision, *RA* rheumatoid arthritis

duration and its two-sided 95% CI were calculated for each treatment group. An event was defined as the discontinuation of treatment, and patients were censored at the end of their follow-up. A log-rank test was performed to compare treatment differences. Multiple testing was adjusted using the Bonferroni correction. The Cox regression model was used to perform univariate analyses on the factors potentially affecting the persistence rate (i.e., age, gender, CCI score, concomitant use and dose of MTX, initial dose of GLM, and number of previous biologic therapies). For each factor, an estimate of hazard ratio (HR) and its associated 95% CI were obtained. Multivariate analysis was performed with all factor variables (without performing model selection). In all analyses, a p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (TS1M6) (SAS/STAT 15.1).

RESULTS

Patient Characteristics

A total of 384,983 records of patients with RA were identified from the MDV database, of which 7524 were prescribed GLM. A total of 39,545 patients were prescribed JAK inhibitors or any other bDMARDs but not GLM and 11,995 of them who met the inclusion/exclusion criteria were considered as the reference cohort for analysis (Fig. 2). Of the 7524 GLM-treated patients, 2283 were never prescribed bDMARDs or JAK inhibitors prior to GLM (naïve), 942 were prescribed one bDMARD or JAK inhibitor prior to GLM [switch (1)], and 322 were prescribed at least two other bDMARDs or JAK inhibitors prior to GLM [switch (≥ 2)]. Figure 2 depicts an overview of the stratified patient demographics of naïve, switch (1), and switch (≥ 2) patients.

The mean age of the patients in the naïve group (67.3 years) was slightly but significantly higher than the mean age of the patients in the switch (overall) group (66.5 years), $p = 0.047$. There was no significant difference in the mean age of patients in the switch (1) group ($p = 0.106$) versus the switch (≥ 2) group ($p = 0.717$). The majority of patients were women (naïve group, 78.84%; switch group, 81.41%) and switched patients had slightly higher CCI scores (CCI score of 3–5, naïve group [23.04%] vs switch group [30.30%]) and had higher morbidity than naïve patients at baseline (Table 1). Patients in the switch (1) group had a significantly higher rate of congestive heart failure ($p = 0.010$), peripheral vascular diseases ($p = 0.009$), chronic lung diseases ($p < 0.001$), ulcers ($p = 0.003$), diabetes without chronic complications ($p = 0.005$), renal disease ($p = 0.030$), and acquired immune deficiency syndrome/human immunodeficiency virus (AIDS/HIV) ($p = 0.028$) than the naïve group. However, none of the differences were significant when compared to patients in the switch (≥ 2) group ($p > 0.05$). The prevalence of hemiplegia or paraplegia (0.57%) was found only in naïve patients. A higher percentage of naïve patients (naïve group 37.14% vs overall switch group 22.47%) were receiving concomitant high dose MTX (> 8 mg/week), while more switched patients received no MTX (MTX free, 41.46%) or low dose (≤ 8 mg/week) of concomitant MTX (36.08%). A high proportion of naïve patients (80.29% vs overall switch group 70.02%) used 50 mg of GLM as their first dose, while a high proportion of switched patients (overall switch group 29.35% vs naïve group 19.23%) used 100 mg of GLM as their first dose.

GLM Persistence in Naïve vs Switch Groups

As per the Kaplan–Meier analyses, the persistence rate of GLM naïve patients was 58.78% (95% CI 56.73–60.77) at 1 year, 32.08% (95% CI 29.93–34.25) at 3 years, 21.42% (95% CI 18.96–23.99) at 5 years, and 11.36% (95% CI 7.54–16.02) at 7 years (Fig. 3). The persistence rate of GLM decreased with the number of drug switches compared to naïve patients. The persistence rate for switch (1) patients was 49.04% (95% CI 45.81–52.19) at 1 year, 30.29% (95% CI 27.17–33.45) at 3 years, 18.76% (95% CI 15.49–22.27) at 5 years, and 11.62% (95% CI 7.70–16.41) at 7 years. In switch (≥ 2) patients,

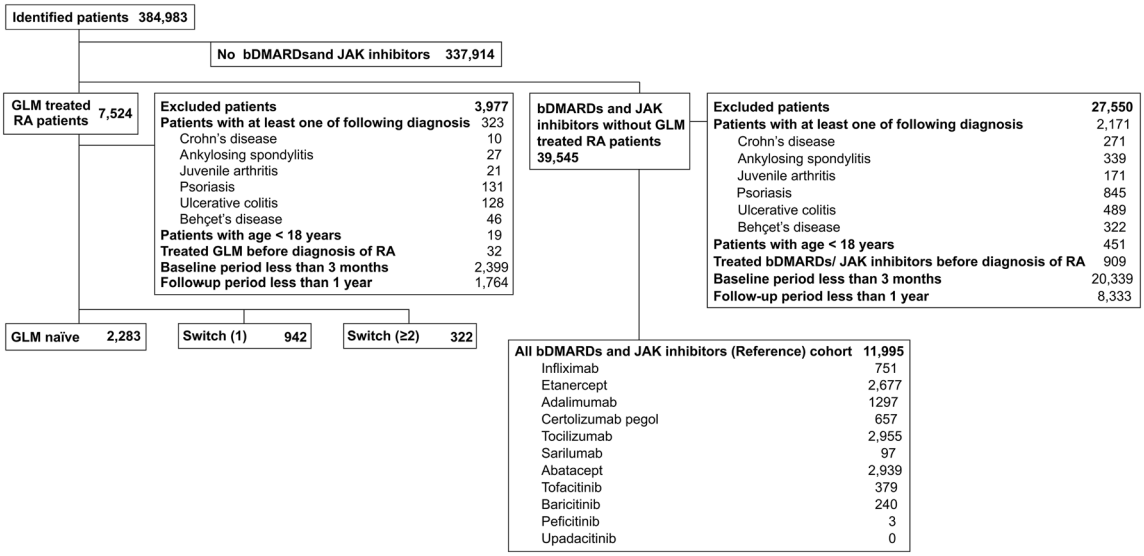


Fig. 2 Flow diagram of patient disposition demonstrating the number of patients included in each population of the GLM cohort study or all bDMARDs and JAK inhibitor cohort study. *bDMARDs* biologic disease-modifying antirheumatic drugs, *GLM* golimumab, *JAK* Janus kinase, *RA* rheumatoid arthritis

the rates were 45.34% (95% CI 39.83–50.68%) at 1 year, 19.12% (95% CI 14.56–24.15) at 3 years, 13.98% (95% CI 9.49–19.31) at 5 years, and 5.24% (95% CI 1.40–13.05%) at 7 years (Fig. 3). The Kaplan–Meier analysis showed longer persistence in the GLM naïve group compared with the switch (1) group ($p < 0.001$). Similar significant difference was also observed when the switch (1) group was compared with the switch (≥ 2) group ($p < 0.001$). The median time to discontinuation of GLM was shorter in the switch groups compared to the naïve group [naïve, 529 days; switch (1), 358 days; switch (≥ 2), 319 days]. The time to discontinuation of GLM, especially in the naïve group (529 days), was comparable or longer than the reference cohort that includes other bDMARDs and JAK inhibitors (329 days) (Fig. 3).

Effect of Baseline Factors on GLM Persistence

The Cox HR analysis was used to examine baseline demographic and clinical factors affecting GLM persistence at each GLM administration timing (Table 2). The GLM persistence rate was significantly increased by age. In the GLM-naïve group patients aged between 61 and 75 years had an increased GLM persistence rate (HR 0.84, $p = 0.008$). However, age had no significant effect on persistence rate in patients aged > 75 years or in the switch groups. Gender was associated with an increase in the GLM persistence rate in the naïve group (HR 0.86, $p = 0.019$), but there was no significant difference in switch groups. Both high-dose (> 8 mg/week) and low-dose (≤ 8 mg/week) concomitant use of MTX were significant factors in increasing the GLM persistence rate in the naïve and switch (1) groups. The HR for concomitant MTX high dose was 0.71 ($p < 0.001$) for the naïve group and 0.78 ($p < 0.01$) for switch (1) group. The HR for concomitant MTX low dose was 0.66 ($p < 0.001$) for the naïve group and 0.74 ($p < 0.001$) for the switch (1) group. CCI scores of 3–5 had higher hazards of medication discontinuation and thus were less persistent compared to the reference group in the naïve group (HR 1.19, $p = 0.005$) and switch group (1) (HR 1.18, $p = 0.0048$). Regarding the initial dose of GLM, a dose of 100 mg significantly reduced the GLM persistence rate in the switch (1) group

Table 1 Demographics and clinical baseline characteristics

	GLM cohort							
	GLM naïve	Switch (total)		Switch (1)		Switch (≥ 2)		Reference cohort
	N = 2283	*N* = 1264	*p* value (vs naïve)	*N* = 942	*p* value (vs naïve)	*N* = 322	*p* value (vs naïve)	*N* = 11,995
Age (mean ± SD)	67.3 ± 12.60	66.5 ± 12.40	0.047	66.5 ± 12.50	0.106	66.4 ± 12.20	0.717	63.7 ± 14.00
≤ 60 years	585 (25.62%)	352 (27.85%)		264 (28.03%)		88 (27.33%)		4246 (35.40%)
61–75 years	1061 (46.47%)	597 (47.23%)		437 (46.39%)		160 (49.69%)		5221 (43.53%)
> 75 years	637 (27.90%)	315 (24.92%)		241 (25.58%)		74 (22.98%)		2528 (21.08%)
Gender			0.069		0.215		0.330	
Male	483 (21.16%)	235 (18.59%)		181 (19.21%)		54 (16.77%)		2672 (22.28%)
Female	1800 (78.84%)	1029 (81.41%)		761 (80.79%)		268 (83.23%)		9323 (77.72%)
CCI score (mean ± SD)	2.1 ± 1.40	2.4 ± 1.60	< 0.001	2.3 ± 1.60	< 0.001	2.5 ± 1.70	0.105	2.2 ± 1.60
≤ 2	1674 (73.32%)	821 (64.95%)		628 (66.67%)		193 (59.94%)		8432 (70.30%)
3–5	526 (23.04%)	383 (30.30%)		276 (29.30%)		107 (33.23%)		3009 (25.09%)
> 5	83 (3.64%)	60 (4.75%)		38 (4.03%)		22 (6.83%)		554 (4.62%)
Comorbidity								
Myocardial infarction	34 (1.49%)	15 (1.19%)	0.46	13 (1.38%)	0.814	2 (0.62%)	0.278	173 (1.44%)
Congestive heart failure	174 (7.62%)	141 (11.16%)	< 0.001	98 (10.40%)	0.010	43 (13.35%)	0.147	1209 (10.08%)
Peripheral vascular disease	126 (5.52%)	95 (7.52%)	0.018	75 (7.96%)	0.009	20 (6.21%)	0.304	726 (6.05%)
Cerebrovascular disease	120 (5.26%)	77 (6.09%)	0.298	60 (6.37%)	0.210	17 (5.28%)	0.480	740 (6.17%)
Dementia	22 (0.96%)	12 (0.95%)	0.967	9 (0.96%)	0.983	3 (0.93%)	0.970	82 (0.68%)
Chronic lung disease	345 (15.11%)	294 (23.26%)	< 0.001	213 (22.61%)	< 0.001	81 (25.16%)	0.351	1961 (16.35%)
Ulcer	513 (22.47%)	364 (28.80%)	< 0.001	258 (27.39%)	0.003	106 (32.92%)	0.058	2814 (23.46%)
Chronic liver disease	366 (16.03%)	231 (18.28%)	0.087	166 (17.62%)	0.268	65 (20.19%)	0.304	1931 (16.10%)

Table 1 continued

	GLM cohort							
	GLM naïve	Switch (total)		Switch (1)		Switch (≥ 2)		Reference cohort
	N = 2283	*N* = 1264	*p* value (vs naïve)	*N* = 942	*p* value (vs naïve)	*N* = 322	*p* value (vs naïve)	*N* = 11,995
Diabetes without chronic complication	93 (4.07%)	87 (6.88%)	< 0.001	60 (6.37%)	0.005	27 (8.39%)	0.217	713 (5.94%)
Hemiplegia or paraplegia	13 (0.57%)	0 (0.00%)	0.007	0 (0.00%)	0.02	0 (0.00%)	–	28 (0.23%)
Renal disease	87 (3.81%)	70 (5.54%)	0.017	52 (5.52%)	0.03	18 (5.59%)	0.962	577 (4.81%)
Diabetes with chronic complication	77 (3.37%)	45 (3.56%)	0.769	33 (3.50%)	0.853	12 (3.73%)	0.852	343 (2.86%)
Any malignancy	126 (5.52%)	74 (5.85%)	0.678	52 (5.52%)	0.999	22 (6.83%)	0.387	830 (6.92%)
Moderate or severe liver disease	7 (0.31%)	3 (0.24%)	0.709	3 (0.32%)	0.956	0 (0.00%)	0.311	42 (0.35%)
Metastatic solid tumor	13 (0.57%)	8 (0.63%)	0.813	4 (0.42%)	0.606	4 (1.24%)	0.11	97 (0.81%)
AIDS/HIV	0 (0.00%)	2 (0.16%)	0.057	2 (0.21%)	0.028	0 (0.00%)	0.408	9 (0.08%)
MTX treatment			< 0.001		< 0.001		0.001	
MTX free	704 (30.84%)	524 (41.46%)		363 (38.54%)		161 (50.00%)		5504 (45.89%)
MTX high (> 8 mg/week)	848 (37.14%)	284 (22.47%)		224 (23.78%)		60 (18.63%)		3560 (29.68%)
MTX low (≤ 8 mg/week)	731 (32.02%)	456 (36.08%)		355 (37.69%)		101 (31.37%)		2931 (24.44%)
Initial dose of GLM			< 0.001		< 0.001		0.002	
50 mg	1833 (80.29%)	885 (70.02%)		684 (72.61%)		201 (62.42%)		–
100 mg	439 (19.23%)	371 (29.35%)		252 (26.75%)		119 (36.96%)		–

Table 1 continued

	GLM cohort							
	GLM naïve	Switch (total)		Switch (1)		Switch (≥ 2)		Reference cohort
	N = 2283	*N* = 1264	*p* value (vs naïve)	*N* = 942	*p* value (vs naïve)	*N* = 322	*p* value (vs naïve)	*N* = 11,995
Others	11 (0.48%)	8 (0.63%)		6 (0.64%)		2 (0.62%)		–

AIDS/HIV acquired immune deficiency syndrome/human immunodeficiency virus, *bDMARDs* biologic disease-modifying anti-rheumatic drugs, *CCI* Charlson Comorbidity Index, *GLM* golimumab, *JAK* Janus kinase, *MTX* methotrexate

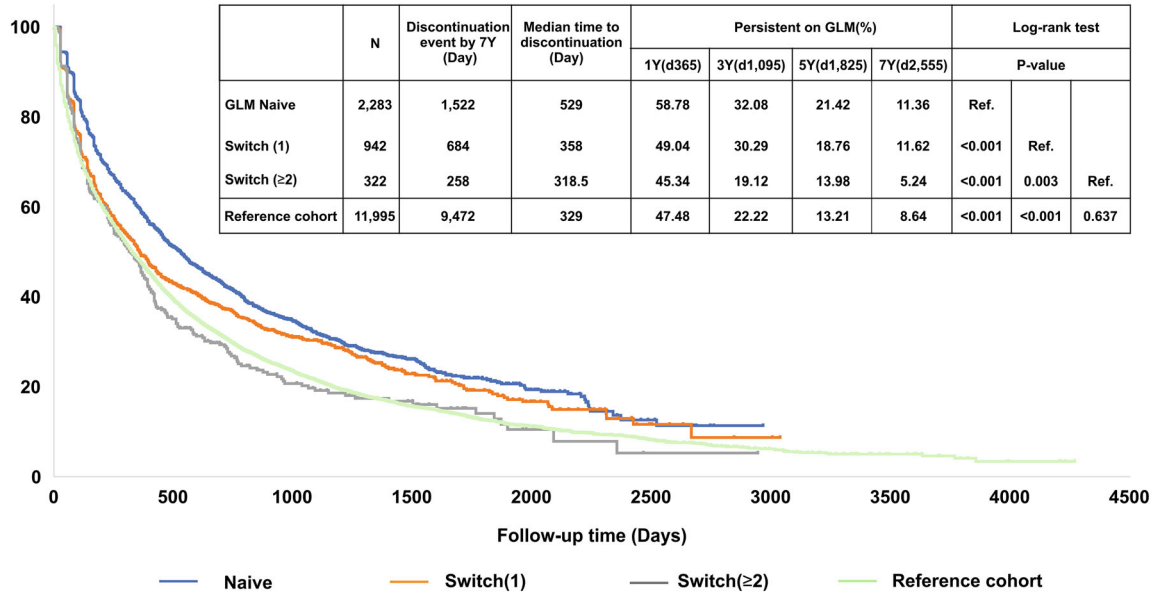
compared to patients receiving a dose of 50 mg (HR 1.23, $p = 0.022$). There was no significant difference in the naïve group amongst the patients taking a dose of 100 mg or 50 mg. Overall, in the switch (≥ 2) group, there was no statistically significant influence of age, gender, CCI score (Supplementary Table S4), concomitant MTX, or initial dose of GLM on persistence rate.

Baseline Factors Predictive of > 5-Year Persistence with GLM

Logistic regression analysis was used to identify baseline factors associated with achieving GLM treatment persistence for more than 5 years (Table 3). Age (61–75 years), gender (HR 0.86, $p = 0.002$), concomitant MTX high dose (HR 0.73, $p < 0.001$), concomitant MTX low dose (HR 0.70, $p < 0.001$) were positively associated with GLM persistence for over 5 years. Conversely, CCI score of 3–5 (HR 1.17, $p < 0.001$) and score > 5 (HR 1.29, $p = 0.010$), an initial GLM dose of 100 mg (HR 1.14, $p = 0.009$), one prior biologic use (HR 1.14, $p = 0.006$) or two or more prior biologics use (HR 1.31, $p < 0.001$) were identified as factors negatively associated with GLM persistence for over 5 years.

Effect of Prior Biologics on GLM Persistence

To analyze whether the persistence of GLM was altered by the use of bDMARDs or JAK inhibitors prior to GLM, Kaplan–Meier analysis of each bDMARD or JAK inhibitor subgroup was performed for up to 7 years (Fig. 4). Although there were no significant differences in patient background between the subgroups (Table 4), the duration of GLM for each subgroup was as follows in descending order (Fig. 4): infliximab (IFX), 602 days (95% CI 398–882); adalimumab (ADA), 427 days (95% CI 259–693); abatacept (ABT), 355 days (95% CI 280–469); tofacitinib (TOF), 341 days (95% CI 28–not reached); etanercept (ETN), 266 days (95% CI 176–410); certolizumab pegol (CEL), 258 days (95% CI 154–772); tocilizumab (TCZ), 214 days (95% CI



	N	Discontinuation event by 7Y (Day)	Median time to discontinuation (Day)	Persistent on GLM(%)				Log-rank test		
				1Y(d365)	3Y(d1,095)	5Y(d1,825)	7Y(d2,555)	P-value		
GLM Naive	2,283	1,522	529	58.78	32.08	21.42	11.36	Ref.		
Switch (1)	942	684	358	49.04	30.29	18.76	11.62	<0.001	Ref.	
Switch (≥2)	322	258	318.5	45.34	19.12	13.98	5.24	<0.001	0.003	Ref.
Reference cohort	11,995	9,472	329	47.48	22.22	13.21	8.64	<0.001	<0.001	0.637

Fig. 3 Persistence of GLM treatments stratified by the number of prior bDMARDs. A Kaplan–Meier analysis was conducted to assess persistence with GLM treatment during the MDV cohort surveillance period in relation to the number of previous bDMARDs (0, 1, or ≥ 2). Kaplan–Meier curves were compared with the log-rank test, using the subgroup who had previously received one bDMARD as a reference. The log-rank *p* values were adjusted for multiplicity by using Bonferroni correction. Descriptive statistics are presented in the table. Reference cohort: all bDMARDs and JAK inhibitors without GLM cohort. *bDMARDs* biologic disease-modifying anti-rheumatic drugs, *GLM* golimumab, *JAK* Janus kinase, *RA* rheumatoid arthritis

154–302); and sarilumab (SAR), 196 days (95% CI 86–225).

GLM persistence rates by subgroup over time at 1, 3, 5, and 7 years were IFX (59%, 38%, 16%, 11%), ETN (45%, 28%, 20, 13%), ADA (54%, 54%, 24%, 13%), CEL (49%, 49%. 29%, 29%), TCZ (38%, 38%, 14%, 11%), SAR (0%, 0%, 0%, 0%), ABT (48%, 48%, 18%, 9%), TOF (47%, 47%, 31%, 31%), and BAR (80%, 80%, 53%, 53%), respectively.

Furthermore, using the IFX subgroup with the longest persistence rate as a reference, the log-rank test with Bonferroni correction was used to analyze the persistence rate of each subgroup up to 7 years. The results showed significant differences in TCZ ($p = 0.001$), SAR ($p = 0.025$), and TOF ($p = 0.041$), indicating that switching from these drugs to GLM significantly reduced the persistence rate compared to switching from IFX to GLM (Fig. 4). After switching from other drugs to GLM, the persistence rate was lower in groups with high MTX-free rates (Table 4). In particular, in the naïve and switch (1) groups, the persistence of the GLM with MTX was improved (Fig. 5). Amongst the GLM naïve population, the persistence rate in the MTX high group was 63.92%, 34.85%, 21.58%, and 10.66%; in the MTX low group, it was 63.89%, 38.41%, 29.22%, and 21.65% when compared to MTX-free group (47.3%, 21.89%, 12.47%, and 3.57%) at 1, 3, 5, and 7 years, respectively. Similarly, in the switch (1) population, the persistence rate in the MTX high group was 54.02%, 37.01%, 21.8%, and 9.91%; in the MTX low group, it was 53.52%, 35.36%, 27.13%, and 18.41% when compared to the MTX-free group (41.6%, 21.07%, 9.21%, and 9.21%) at 1, 3, 5, and 7 years, respectively (Supplementary Table S4).

DISCUSSION

The current analysis of the GLM persistence in patients with RA provides an update of 7 years of long-term hospital claims cohort data that

Table 2 Factors affecting persistence in the naïve, switch (1), or switch (≥ 2) groups and regression results

	GLM naïve		Switch (1)		Switch (≥ 2)	
	Multivariate analysis		Multivariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age						
≤ 60 years	Reference		Reference		Reference	
61–75 years	0.84 (0.74–0.96)	0.008	1 (0.83–1.20)	0.990	0.91 (0.67–1.22)	0.516
> 75 years	0.98 (0.85–1.13)	0.811	0.96 (0.78–1.19)	0.726	0.91 (0.63–1.32)	0.623
Gender						
Male	Reference		Reference		Reference	
Female	0.86 (0.76–0.98)	0.019	0.86 (0.71–1.04)	0.121	0.81 (0.58–1.12)	0.207
CCI score						
≤ 2	Reference		Reference		Reference	
3–5	1.19 (1.06–1.34)	0.005	1.18 (1.00–1.39)	0.048	1.06 (0.81–1.38)	0.682
> 5	1.28 (0.99–1.67)	0.060	1.4 (0.98–2.02)	0.065	1.05 (0.64–1.71)	0.847
MTX treatment						
MTX-free	Reference		Reference		Reference	
MTX high	0.71 (0.62–0.81)	< 0.001	0.78 (0.63–0.96)	0.018	0.76 (0.53–1.08)	0.122
MTX low	0.66 (0.57–0.75)	< 0.001	0.74 (0.61–0.89)	0.001	0.83 (0.61–1.13)	0.233
Initial dose of GLM						
50 mg	Reference		Reference		Reference	
100 mg	1.08 (0.95–1.24)	0.233	1.23 (1.03–1.46)	0.022	1.16 (0.89–1.53)	0.274

CCI Charlson Comorbidity Index, *CI* confidence interval, *GLM* golimumab, *MTX* methotrexate

has not previously been reported in Japan. In a previous study in naïve Japanese patients, MDV data was analyzed, and high RA persistence rates for GLM (100%) were reported at 1 year; however, this study included a shorter prescription history of 3 years (2012–2014), only 1.5 years of GLM follow-up period, and small sample size (GLM naïve, $n = 27$; switch, $n = 87$) [15]. In contrast, a large population of patients with RA from long-term prescription records for the period of 13 years (2008–2020) was analyzed in this study. This study demonstrated that the persistence rates for the GLM naïve or switch (1) patients were approximately 60% in 1 year, 30% in 3 years, 20% in 5 years, and 10% in 7 years, and with these GLM subgroups the persistence rates were found to be significantly improved compared to all bDMARDs or JAK inhibitors subgroup (Fig. 3). These persistence rates were comparable to or lower than those of reported in Japanese and global studies [7, 8, 20–23]. However, in this study, the persistence rate for GLM was comparable to the reference cohort, which included all other bDMARDs and JAK inhibitors that have recently been approved in Japan as oral agents (Fig. 3). Furthermore, a 6-year retrospective observational study of GLM in Japan reported the persistence rate of GLM as 66.3%, 48.3%, and 24.5% at 12, 36, and 72 months, respectively [24], which are in

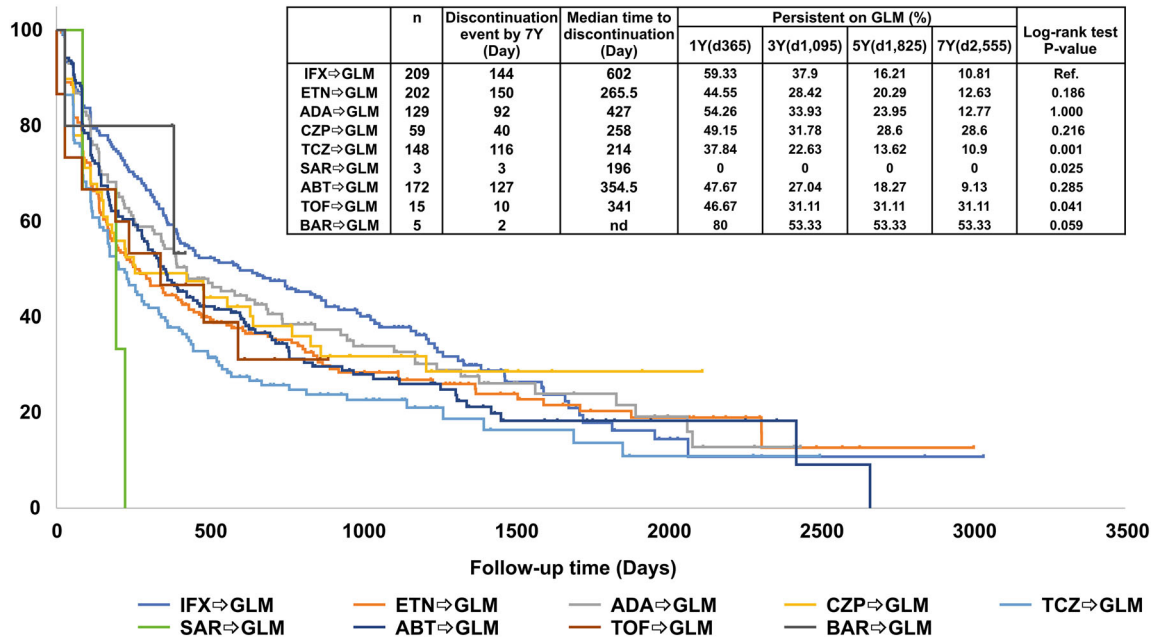
Table 3 Univariate and multivariate Cox regression analysis to identify patient characteristic variables associated with the likelihood of long-term persistence (> 5 years) with GLM treatment

	Univariate analysis Hazard ratio (95% CI)	*p* value	Multivariate analysis Hazard ratio (95% CI)	*p* value
Age				
≤ 60 years	Reference		Reference	
61–75 years	0.95 (0.86–1.04)	0.269	0.90 (0.81–0.99)	0.027
> 75 years	1.11 (1.00–1.24)	0.055	0.97 (0.87–1.09)	0.592
Gender				
Male	Reference		Reference	
Female	0.85 (0.77–0.94)	0.001	0.86 (0.78–0.95)	0.002
CCI score				
≤ 2	Reference		Reference	
3–5	1.25 (1.15–1.37)	< 0.001	1.17 (1.07–1.28)	< 0.001
> 5	1.48 (1.22–1.79)	< 0.001	1.29 (1.06–1.57)	0.010
MTX treatment				
MTX-free	Reference		Reference	
MTX high	0.67 (0.61–0.73)	< 0.001	0.73 (0.66–0.82)	< 0.001
MTX low	0.64 (0.58–0.71)	< 0.001	0.7 (0.63–0.77)	< 0.001
Initial dose of GLM				
50 mg	Reference		Reference	
100 mg	1.35 (1.23–1.48)	< 0.001	1.14 (1.03–1.26)	0.009
Number of previous biologic therapies				
GLM naïve	Reference		Reference	
Switch (1)	1.18 (1.08–1.30)	< 0.001	1.14 (1.04–1.25)	0.006
Switch (≥ 2)	1.46 (1.28–1.67)	< 0.001	1.31 (1.15–1.50)	< 0.001

CCI Charlson Comorbidity Index, *CI* confidence interval, *GLM* golimumab, *MTX* methotrexate

agreement with the persistence rates observed in this study. Therefore, the results presented here may be considered as a real-world indicator of the GLM persistence in Japan.

The possible reasons for the variation in persistence rates in the Japanese studies using the same database includes changes in medical technology over time, changes in guidelines, and other medical information such as remission criteria and timing of judgment, as well as an increase in treatment choices [25]. Previous reports using MDV limited the choice of biologics to five drugs (GLM, ETN, ADA, IFX, TCZ, and ABT). In this analysis, we have extended the drug list with the addition of data on SAR, CPZ, and JAK inhibitors (TOF and BAR). Additionally, advances in methods for assessing disease activity in RA and setting treatment goals that aim for higher treatment satisfaction and deeper remission have resulted in earlier judgments



	n	Discontinuation event by 7Y (Day)	Median time to discontinuation (Day)	Persistent on GLM (%)				Log-rank test P-value
				1Y(d365)	3Y(d1,095)	5Y(d1,825)	7Y(d2,555)	
IFX⇨GLM	209	144	602	59.33	37.9	16.21	10.81	Ref.
ETN⇨GLM	202	150	265.5	44.55	28.42	20.29	12.63	0.186
ADA⇨GLM	129	92	427	54.26	33.93	23.95	12.77	1.000
CZP⇨GLM	59	40	258	49.15	31.78	28.6	28.6	0.216
TCZ⇨GLM	148	116	214	37.84	22.63	13.62	10.9	0.001
SAR⇨GLM	3	3	196	0	0	0	0	0.025
ABT⇨GLM	172	127	354.5	47.67	27.04	18.27	9.13	0.285
TOF⇨GLM	15	10	341	46.67	31.11	31.11	31.11	0.041
BAR⇨GLM	5	2	nd	80	53.33	53.33	53.33	0.059

Fig. 4 Persistence of GLM treatments stratified by first-line bDMARD therapy. The Kaplan–Meier analysis was employed to assess persistence with GLM treatment during the MDV cohort surveillance period stratified by the first-line bDMARD (IFX, ETN, ADA, CPZ, TCZ, SAR, ABT, TOF, BAR). Each subgroup curve was compared with the IFX curve by log-rank test and *p* values were adjusted for multiplicity using Bonferroni correction. Descriptive statistics are presented in the table. *GLM* golimumab, *IFX* infliximab *ADA* adalimumab, *ETN* etanercept, *CPZ* certolizumab, *TCZ* tocilizumab, *SAR* sarilumab, *ABT* abatacept, *TOF* tofacitinib, *BAR* baricitinib, *bDMARDs* biologic disease-modifying anti-rheumatic drugs, *JAK* Janus kinase, *MDV* Medical Data Vision

of drug effectiveness and shorter duration of each drug.

Various randomized clinical trials assessed the GLM persistence rates in the Japanese population. The 3-year persistence rate of GLM in the study of MTX-IR patients (GO-FORTH) was 73.2% [23], and the 120-week persistence rate in the study of csDMARD-IR patients (GO-MONO) was 73.1% [22]. Also, a 24-week PMS study has reported the GLM persistence after switching from other biologics with persistence rates of 84.4%, 78.2%, 72.9%, 72.7%, and 72.3% for IFX, ADA, ABT, ETN, and TCZ, respectively [26].

In this study, the factors affecting the long-term use of GLM were age (61–75 years), gender (female), and the concomitant use of MTX as extension factors. On the contrary, CCI score of ≥ 3, initial GLM dose of 100 mg, and the number of previous biologics switches were shortening factors (Tables 2 and 3). It has been shown that younger patients generally tend to have a higher persistence rate of TNF agents than elderly patients [27, 28], and in a previous MDV analysis, both gender and CCI showed a similar trend in comparison with bDMARDs overall [15]. Although other studies have shown that CCI has no effect on the persistence of biologic agents [17, 29], it is possible that many clinicians were attempting to make the best possible use of one agent because of the limited drug options available at the time. In the current analysis, the presence or absence of concomitant MTX and the initial dose of GLM were newly identified as factors affecting the persistence of GLM. In the Japanese PMS study, GLM combined with MTX clearly improved the disease activity index (DAS28-ESR [erythrocyte sedimentation rate]) and the persistence rate of GLM in patients with RA [30], and the current study supported these results. Although the same PMS study showed that the dose of GLM (50 or 100 mg) has no effect on the persistence

Table 4 Characteristics of patient demographics and clinical baseline characteristics of the switch (1) group

	Total	bDMARDs							JAK inhibitors			
		IFX⇒GLM	ETN⇒GLM	ADA⇒GLM	CPZ⇒GLM	TCZ⇒GLM	SAR⇒GLM	ABT⇒GLM	TOF⇒GLM	BAR⇒GLM	PEF⇒GLM	UPA ⇒GLM
	N = 942	*N* = 209	*N* = 202	*N* = 129	*N* = 59	*N* = 148	*N* = 3	*N* = 172	*N* = 15	*N* = 5	*N* = 0	*N* = 0
Age (mean ± SD)	66.5 ± 12.50	63.8 ± 12.40	68.2 ± 12.30	64.5 ± 12.40	64.0 ± 14.70	65.1 ± 12.40	73.0 ± 7.80	71.6 ± 10.50	67.3 ± 10.30	60.0 ± 13.70	–	–
≤ 60 years	264 (28.03%)	69 (33.01%)	50 (24.75%)	45 (34.88%)	22 (37.29%)	45 (30.41%)	0 (0.00%)	26 (15.12%)	4 (26.67%)	3 (60.00%)	0	0
61–75 years	437 (46.39%)	107 (51.20%)	91 (45.05%)	59 (45.74%)	23 (38.98%)	73 (49.32%)	1 (33.33%)	74 (43.02%)	8 (53.33%)	1 (20.00%)	0	0
> 75 years	241 (25.58%)	33 (15.79%)	61 (30.20%)	25 (19.38%)	14 (23.73%)	30 (20.27%)	2 (66.67%)	72 (41.86%)	3 (20.00%)	1 (20.00%)	0	0
Gender												
Male	181 (19.21%)	44 (21.05%)	31 (15.35%)	25 (19.38%)	12 (20.34%)	32 (21.62%)	2 (66.67%)	31 (18.02%)	4 (26.67%)	0 (0.00%)	0	0
Female	761 (80.79%)	165 (78.95%)	171 (84.65%)	104 (80.62%)	47 (79.66%)	116 (78.38%)	1 (33.33%)	141 (81.98%)	11 (73.33%)	5 (100.00%)	0	0
CCI score (mean ± SD)	2.3 ± 1.60	2.3 ± 1.40	2.4 ± 1.60	2.2 ± 1.60	1.9 ± 1.50	2.5 ± 1.60	1.7 ± 1.20	2.5 ± 1.70	2.2 ± 1.40	3.0 ± 1.90	–	–
≤2	628 (66.67%)	131 (62.68%)	136 (67.33%)	97 (75.19%)	47 (79.66%)	94 (63.51%)	2 (66.67%)	108 (62.79%)	10 (66.67%)	3 (60.00%)	0	0
3–5	276 (29.30%)	73 (34.93%)	57 (28.22%)	28 (21.71%)	10 (16.95%)	46 (31.08%)	1 (33.33%)	55 (31.98%)	4 (26.67%)	2 (40.00%)	0	0
> 5	38 (4.03%)	5 (2.39%)	9 (4.46%)	4 (3.10%)	2 (3.39%)	8 (5.41%)	0 (0.00%)	9 (5.23%)	1 (6.67%)	0 (0.00%)	0	0
Comorbidity												
Myocardial infarction	13 (1.38%)	4 (1.91%)	5 (2.48%)	1 (0.78%)	0 (0.00%)	3 (2.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0	0
Congestive heart failure	98 (10.40%)	21 (10.05%)	28 (13.86%)	3 (2.33%)	4 (6.78%)	16 (10.81%)	0 (0.00%)	24 (13.95%)	2 (13.33%)	0 (0.00%)	0	0
Peripheral vascular disease	75 (7.96%)	14 (6.70%)	21 (10.40%)	5 (3.88%)	3 (5.08%)	16 (10.81%)	0 (0.00%)	15 (8.72%)	1 (6.67%)	0 (0.00%)	0	0
Cerebrovascular disease	60 (6.37%)	11 (5.26%)	12 (5.94%)	13 (10.08%)	0 (0.00%)	8 (5.41%)	0 (0.00%)	12 (6.98%)	3 (20.00%)	1 (20.00%)	0	0
Dementia	9 (0.96%)	1 (0.48%)	5 (2.48%)	0 (0.00%)	0 (0.00%)	1 (0.68%)	0 (0.00%)	2 (1.16%)	0 (0.00%)	0 (0.00%)	0	0
Chronic lung disease	213 (22.61%)	39 (18.66%)	56 (27.72%)	31 (24.03%)	10 (16.95%)	30 (20.27%)	0 (0.00%)	44 (25.58%)	2 (13.33%)	1 (20.00%)	0	0
Ulcer	258 (27.39%)	61 (29.19%)	53 (26.24%)	27 (20.93%)	10 (16.95%)	48 (32.43%)	0 (0.00%)	52 (30.23%)	4 (26.67%)	3 (60.00%)	0	0
Chronic liver disease	166 (17.62%)	43 (20.57%)	30 (14.85%)	20 (15.50%)	9 (15.25%)	29 (19.59%)	0 (0.00%)	31 (18.02%)	3 (20.00%)	1 (20.00%)	0	0
Diabetes without chronic complication	60 (6.37%)	12 (5.74%)	14 (6.93%)	5 (3.88%)	4 (6.78%)	15 (10.14%)	0 (0.00%)	9 (5.23%)	1 (6.67%)	0 (0.00%)	0	0

Table 4 continued

	Total	bDMARDs						JAK inhibitors			
		IFX⇒GLM	ETN⇒GLM	ADA⇒GLM	CPZ⇒GLM	TCZ⇒GLM	SAR⇒GLM	ABT⇒GLM	TOF⇒GLM	BAR⇒GLM	PEF⇒GLM	UPA ⇒GLM
	N = 942	*N* = 209	*N* = 202	*N* = 129	*N* = 59	*N* = 148	*N* = 3	*N* = 172	*N* = 15	*N* = 5	*N* = 0	*N* = 0
Hemiplegia or paraplegia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0	0
Renal disease	52 (5.52%)	6 (2.87%)	11 (5.45%)	7 (5.43%)	4 (6.78%)	9 (6.08%)	1 (33.33%)	13 (7.56%)	1 (6.67%)	0 (0.00%)	0	0
Diabetes with chronic complication	33 (3.50%)	6 (2.87%)	8 (3.96%)	4 (3.10%)	1 (1.69%)	9 (6.08%)	0 (0.00%)	3 (1.74%)	0 (0.00%)	2 (40.00%)	0	0
Any malignancy	52 (5.52%)	15 (7.18%)	8 (3.96%)	6 (4.65%)	1 (1.69%)	9 (6.08%)	0 (0.00%)	13 (7.56%)	0 (0.00%)	0 (0.00%)	0	0
Moderate or severe liver disease	3 (0.32%)	2 (0.96%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.58%)	0 (0.00%)	0 (0.00%)	0	0
Metastatic solid tumor	4 (0.42%)	1 (0.48%)	1 (0.50%)	1 (0.78%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.58%)	0 (0.00%)	0 (0.00%)	0	0
AIDS/HIV	2 (0.21%)	0 (0.00%)	0 (0.00%)	1 (0.78%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.58%)	0 (0.00%)	0 (0.00%)	0	0
MTX treatment												
MTX-free	363 (38.54%)	42 (20.10%)	81 (40.10%)	37 (28.68%)	27 (45.76%)	79 (53.38%)	1 (33.33%)	86 (50.00%)	6 (40.00%)	4 (80.00%)	0	0
MTX high	224 (23.78%)	60 (28.71%)	44 (21.78%)	48 (37.21%)	12 (20.34%)	23 (15.54%)	2 (66.67%)	30 (17.44%)	4 (26.67%)	1 (20.00%)	0	0
MTX low	355 (37.69%)	107 (51.20%)	77 (38.12%)	44 (34.11%)	20 (33.90%)	46 (31.08%)	0 (0.00%)	56 (32.56%)	5 (33.33%)	0 (0.00%)	0	0
Initial dose of GLM												
50 mg	684 (72.61%)	150 (71.77%)	165 (81.68%)	111 (86.05%)	35 (59.32%)	100 (67.57%)	1 (33.33%)	112 (65.12%)	9 (60.00%)	1 (20.00%)	0	0
100 mg	252 (26.75%)	57 (27.27%)	37 (18.32%)	17 (13.18%)	23 (38.98%)	48 (32.43%)	2 (66.67%)	59 (34.30%)	5 (33.33%)	4 (80.00%)	0	0
Others	6 (0.64%)	2 (0.96%)	0 (0.00%)	1 (0.78%)	1 (1.69%)	0 (0.00%)	0 (0.00%)	1 (0.58%)	1 (6.67%)	0 (0.00%)	0	0
Patients who had previously received non-TNFi bDMARDs	343 (36.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	148 (100.00%)	3 (100.00%)	172 (100.00%)	15 (100.00%)	5 (100.00%)	0	0

ABT abatacept, *ADA* adalimumab, *AIDS/HIV* acquired immune deficiency syndrome/human immunodeficiency virus, *BAR* baricitinib, *bDMARDs* biologic disease-modifying anti-rheumatic drugs, *CCI* Charlson Comorbidity Index, *CPZ* certolizumab, *ETN* etanercept, *GLM* golimumab, *IFX* infliximab, *JAK* Janus kinase, *MTX* methotrexate, *PEF* peficitinib, *SAR* sarilumab, *SD* standard deviation, *TCZ* tocilizumab, *TOF* tofacitinib, *TNFi* tumor necrosis factor inhibitor, *UPA* upadacitinib

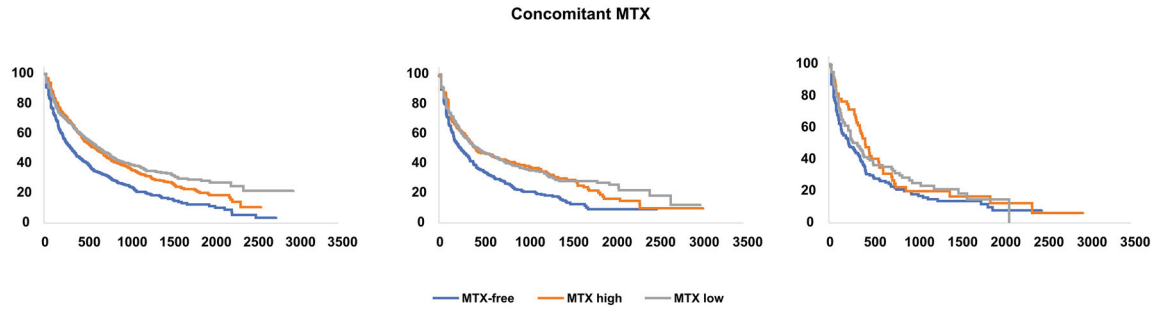


Fig. 5 Persistence by each factor with GLM treatment stratified by the number of prior bDMARDs. A Kaplan–Meier analysis was conducted to assess persistence with GLM treatment during the MDV cohort surveillance period in relation to the number of previous bDMARDs [naïve, switch (1), or switch (≥ 2)]. Kaplan–Meier curves were compared with the log-rank test, using the subgroup who had previously received one bDMARD as a reference. The log-rank *p* values were adjusted for multiplicity by using Bonferroni correction. *GLM* golimumab, *MTX* methotrexate

rate [30], the findings of the current study were based on the initial GLM dose, and the persistence rate may have been affected by the patient's condition at the start of GLM administration. In general, patients who started high-dose administration were expected to have a more severe condition. Furthermore, since GLM has already been approved for use at 100 mg without MTX in Japan, it is possible that the proportion of patients with serious complications was higher than in the group starting with 50 mg. However, we were unable to identify the precise cause of the difference.

It is commonly known that the initial choice of bDMARD influences the clinical response to the next drug when switching bDMARDs, considering the principles of the treat-to-target strategy [9, 31]. With reference to the previous subanalysis of PMS [26], we further provided real-world data on GLM persistence rates in patients with RA who had received primary treatment with another bDMARDs or JAK inhibitors prior to GLM prescription. In a subanalysis of GLM PMS, improvements in clinical signs and symptoms (DAS28-CRP, DAS28-ESR, SDAI [Simplified Disease Activity Index], and CDAI [Clinical Disease Activity Index] scores) were observed in the entire patient population [26]. Several other studies have reported that the reason for discontinuation of the first bDMARD (inefficiency and intolerance) may affect the effectiveness of the second bDMARD [10, 11, 32]. In addition, patients who discontinued the first bDMARD because of adverse events are more likely to respond to the second bDMARD than those who discontinued because of effectiveness-related reasons [13], posing an inherent challenge in interpreting effectiveness and persistence. Several observational cohort studies have demonstrated the effectiveness of switching from one TNF inhibitor to another in actual clinical practice [33–35]. Although evidence is lacking on which bDMARD treatment pattern is most effective, a subanalysis of the PMS that stratified primary bDMARDs prior to switching to GLM was conducted to assess clinical effectiveness, remission rates, and persistence. The results showed that GLM was effective regardless of the type of previous bDMARDs. It was also shown that the persistence rate was the highest when switching from IFX to GLM and was lower when switching from ETN to GLM [26]. Similarly, in the current MDV cohort study, the highest persistence rate was observed when switching from IFX to GLM, and this was confirmed to be reproducible (Fig. 4). Although our analysis does not identify compelling reasons for these results, further research investigating the presence of antibody levels and anti-drug antibodies after IFX treatment and their impact on outcomes would be beneficial to better understand the mechanisms underlying improved drug response and persistence to subsequent bDMARDs. Additionally, it

was noteworthy that in previous subanalyses of PMS, patients switched from ETN to GLM exhibited lower persistence rates than those who switched from IFX, despite having similar baseline characteristics. On the other hand, the results from our study showed that the subgroup of patients who switched to GLM from drugs with different MoA, such as IL-6 inhibitors (TCZ [$p = 0.001$], SAR [$p = 0.025$]) or JAK inhibitor (TOF [$p = 0.041$]), had a significantly lower retention rate than the group switching from IFX. Furthermore, persistence rate after switching from other drugs to GLM in each group was relatively low in the subgroup with a high MTX-free rate (Table 4). A previous PMS study of GLM reported improved persistence in the patient using concomitant MTX irrespective of GLM (50 mg or 100 mg) dose [28]. Unlike clinical trials, in real-world data, GLM may not be used concomitantly with MTX depending on the patient's clinical conditions, which could be the reason for the relatively low persistence in real practice.

Considering the increased number of drug options, switching to bDMARDs with a different MoA is now proposed as a therapeutic option. Also, several lines of evidence from randomized controlled trials [36], retrospective [37–39], and prospective cohort studies [39] suggest that switching to a non-TNF inhibitor may be more effective than looping TNF inhibitors in patients with RA who have not responded adequately to TNF inhibitors.

Conversely, there is limited evidence that TNF inhibitors can adequately control disease activity in patients with RA who have had an inadequate response to non-TNF bDMARDs [40–42]. Although the effectiveness of switching from non-TNF bDMARDs to GLM has been reported in patients with RA who had inadequate response to TCZ [40], we believe that further analysis of the effectiveness of switching from other non-TNF bDMARDs to GLM in actual clinical practice is needed in the future.

Limitations

Several limitations of this study merit comment. The first limitation was the heterogeneous patient population across GLM subgroups. Particularly, among the non-TNF subgroups, the subgroups of anti-IL-6 agents (SAR) and JAK inhibitors (TOF and BAR), which are relatively new therapies, have a much smaller population than the TNF subgroup, which may compromise the statistical power of this study. Furthermore, limitations exist because of the nature of the database which did not allow for the tracing of typical measures of disease activity such as DAS28, the inability to determine the reason for discontinuation of each drug, and the inability to follow up if a patient is transferred. The MDV database includes both inpatient and outpatient data unless the patient has stopped visiting the hospital. Thus, once the patients leave one hospital, data is not available for evaluation, and it remains unclear if the patient has been lost to follow-up or discontinued the treatment. However, the short evaluation period of 24 weeks, which was a limitation in the GLM PMS subanalysis study, has been sufficiently improved in this study. While real-world data provide valuable insights into the context of more drug options and various medical advances, as well as historical background over time, the data presented in this report needs to be understood and interpreted with caution.

CONCLUSIONS

This study demonstrated a high GLM persistence rate with naïve treatment and after switching from other bDMARDs or JAK inhibitor in a real-world clinical setting with a long follow-up period and a large sample size. The long-term persistence rate of GLM was comparable to that reported in real-world clinical practice, but lower persistence rates were observed in patients who switched drugs more frequently than in naïve patients. Age (61–-75 years), gender (female), and concomitant use of MTX were identified as factors associated with long-term persistence of GLM, whereas high CCI score, initial GLM dose (100 mg), and history of use of other biologic agents were shown to be factors associated with shorter persistence rates. Overall, this real-world

evidence can serve as a foundation to develop future treatment strategies; however, further research is needed to optimize specific drug and patient selection.

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Data Availability. We used commercially available hospital claims data from Medical Data Vision Co., Ltd., the data set supporting the conclusions is not publicly available.

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