【 ORIGINAL ARTICLE 】

Long-term Use of Golimumab in Daily Practice for Patients with Rheumatoid Arthritis

Tetsuya Nemoto [1-3], Satoshi Ito [1], Daisuke Kobayashi [1,4], Chinatsu Takai [1], Syunsuke Sakai [1,4],
Youichi Kurosawa [1,4], Eriko Hasegawa [1,4], Ryo Okabayashi [1], Asami Abe [1], Hiroshi Otani [1],
Hyunho Lee [1], Akira Murasawa [1], Ichiei Narita [4], Kiyoshi Nakazono [1], Yoich Toyoshima [1,3],
Katunori Inagaki [3] and Hajime Ishikawa [1]

Abstract:
Objective   To evaluate the effectiveness and drug retention rate of golimumab (GLM) for long-term use in daily practice for patients with rheumatoid arthritis (RA).
Methods   Patients with RA who started GLM therapy with a minimum follow-up period of 52 weeks were included. The patients were divided into a biologic-naïve group and switch group. The disease activity score (DAS) 28-erythrocyte sedimentation rate (ESR) (DAS28-ESR), grip power, and Japanese version of the health assessment questionnaire (J-HAQ) score were assessed. In addition, the treatment continuation rate was evaluated at the final follow-up.
Patients   Sixty-five patients [58 women and 7 men; median (range) age, 69 (61-74) years; median (range) disease duration, 9 (5-16) years] were included. Twenty-eight patients were biologic-naïve (naïve group), and 37 were switched to biologics (switch group).
Results   The median (range) follow-up period was 134 (58-162) weeks. The DAS28-ESR improved from a median (range) of 4.31 (3.52-5.25) to 2.65 (2.28-3.77) in the naïve group and from 4.27 (3.19-4.89) to 2.89 (2.49-3.88) in the switch group. The grip power improved in both groups (p<0.01); however, the J-HAQ score showed no marked improvement in either group. The continuation rates were 22/28 (78.6%) in the naïve group, and 26/37 (70.3%) in the switch group at the final follow-up.
Conclusion   We herein report for the first time that the long-term use of GLM improves the grip power. Improving the grip power may help prevent sarcopenia and frailty in the future. Given the efficacy and high continuation rate, we suggest that GLM would be a well-tolerated treatment option for RA.

Key words: golimumab, disease-modifying anti-rheumatic drugs, rheumatoid arthritis, grip power

Introduction

The emergence of biological disease-modifying anti-rheumatic drugs (bDMARDs), such as golimumab (GLM), has transformed the treatment of rheumatoid arthritis (RA). GLM is a human monoclonal IgG antibody that binds to tumor necrosis factor-alpha (TNF-α) (1). GLM in combination with methotrexate (MTX) has shown efficacy and safety in phase III clinical trials (2-4). In Japan, the GO-FORTH (5) and GO-MONO (6) trials demonstrated the clinical efficacy and safety of GLM in combination with MTX and as monotherapy, respectively. Based on these data, the Japanese Pharmaceuticals and Medical Devices Agency approved GLM (50 and 100 mg) as the fourth anti-TNF-α antibody in 2011 (7); the 100 mg dose is only available in Japan (8).

Sevedbom et al. performed a systematic review to determine the continuation rate of GLM (9). They identified 12 real-world studies; however, only 3 were original articles, whereas the remaining 9 were abstracts from academic conferences (10-12). There have been a few reports of the 100 mg GLM regimen in daily practice administered once every 4 weeks (8, 11, 13); these reports had follow-up periods of up to 52 weeks. Shono (13) compared the clinical safety and efficacy between a bio-naïve and bio-switch group and reported that the improvement in disease activity was similar between the groups at 24 weeks. Although the GO-FORWARD, GO-AFTER, GO-BEFORE, and GO-MONO studies were randomized controlled trials to show the efficacy and safety of GLM from 120 weeks to 5 years, they differed from studies in real clinical settings (2, 14-16).

The European League Against Rheumatism (EULAR) has recommended the short-term use of prednisolone (PSL) to control disease activity (17). Since a high dose of PSL has many adverse effects, reducing the dose is useful (18). MTX plays an important role in the treatment of RA, but it also has side effects (19), causing many patients to wish to taper or discontinue MTX therapy (20).

Since the introduction of the treat-to-target strategy, patients have sought to achieve a high quality of life (QOL). The Japanese version of the health assessment questionnaire (J-HAQ) is an instrument for measuring the physical function and health-related QOL (21).

Sarcopenia was defined as "age-related loss of muscle mass, plus low muscle strength, and/or low physical performance" by the Asian Working Group for Sarcopenia in 2014, with a consensus update in 2019 (22). The diagnostic criterion of "low muscle strength" is defined as a grip power <28 kg for men and <18 kg for women. Sarcopenia enhances the fall burden, decreases healthy life expectancy, and increases healthcare costs (23, 24). Previous reports on the prevalence of sarcopenia have varied; for example, a meta-analysis showed that the prevalence of sarcopenia in patients with RA was 15-32% (25), and Torii et al. reported a prevalence of 37.1% in Japanese patients (23). In addition, Ishikawa et al. reported that the handgrip power in Japanese patients with RA reflects the level of independence in activity of daily living (ADL), and the cut-off value for independent ADL was 136.5 mmHg (11.8 kgw) for women and 152.5 mmHg (13.5 kgw) for men (26). Only one report has described an improvement in the grip power following the use of bDMARDs, with the use of TNF inhibitors for more than one year being shown to improve the grip power in patients with RA (27). We hypothesized that improving the grip power can not only ameliorate inflammation in the upper extremities in patients with RA but also decrease sarcopenia and increase the healthy life expectancy.

We hypothesized that the long-term use of GLM would be safe and effective in bio-naïve and bio-switch patients in real clinical practice and that the use of GLM would facilitate better disease control, reduce the PSL and MTX dosages, and improve the J-HAQ and grip power. Furthermore, we hypothesized that the grip power correlates with the J-HAQ score and Disease Activity Score (DAS) 28-ESR.

Therefore, in the present study, we evaluated the effectiveness and drug continuation rate of long-term use of GLM in bDMARD-naïve and switch patients in clinical practice in order to determine the reason for discontinuation because of a lack of efficacy.

Materials and Methods

We retrospectively analyzed the data of patients with RA administered GLM at Niigata Rheumatic Center from October 2011 to March 2015. Sixty-five patients (58 women and 7 men) started GLM therapy during this period. All patients were followed up for more than 52 weeks. Data were collected in March 2016 and retrospectively analyzed (Table 1). The patients were divided into bDMARD "naïve" and "switch" groups based on their history of use.

Informed consent was obtained in the form of an opt-out on a poster. No patients were excluded. Signed informed consent was not required by the ethics committee because this was a retrospective study. This study was performed according to Declaration of Helsinki and was approved by the Niigata Rheumatic Center ethics committee.

The diagnosis of RA was based on the 2010 American College of Rheumatology/EULAR classification criteria (28). Patients who had previously used GLM or had congestive heart failure, active tuberculosis, or active infectious diseases were excluded. The GLM induction and dose were decided by discussion between the treating doctor and the patient based on the EULAR recommendations for the management of RA (17). Although 50 mg of GLM is recommended to be used with MTX in Japan (20), we used 50 mg of GLM without MTX for 2 patients in the naïve group and 6 patients in the switch group. GLM was injected subcutaneously every four weeks at the hospital by the medical staff.

We evaluated the age, sex, follow-up period, and history of bDMARDs use, MTX use, and corticosteroid use as patients' baseline characteristics. The RA status was evaluated at 0 and 52 weeks and at the final follow-up based on the following: DAS28-ESR, MTX dose, and PSL dose. The grip power and J-HAQ were also assessed to determine the improvement in the ADL (26). The average grip power of both hands was measured using a mercury dynamometer, which was able to measure from 0 to 300 mmHg (28.9 kg). The patients were divided into bDMARD naïve and switch groups and compared with each other.

The continuation rate of GLM was compared between the groups. In addition, we compared the continuation rate of GLM in patients who had and had not been administered MTX. The demographic parameters of patients who did and did not use MTX were also compared.

Statistical analyses

Statistical analyses were performed using the JMP® 14

Table 1.   Characteristics of Patients in the Naïve and Switch Groups.

	Total (n=65)	Naïve (n=28)	Switch (n=37)	p value
Female, n (%)	58 (89%)	25 (89%)	33 (89%)	0.990
Age, years	69 (61-74)	68 (60-71)	70 (60-76)	0.180
Disease duration of RA, years	9 (5-16)	10 (2-20)	9 (7-16)	0.418
Follow up period	134 (58-162)	127 (79-148)	142 (80-170)	0.310
Swollen joint count	3 (1-6)	3 (1-6)	2 (0-6)	0.414
Tender joint count	3 (1-6)	4 (1-8)	2 (1-5)	0.149
Patient's global VAS score, mm	46 (23-59)	47 (25-60)	46 (21-59)	0.842
Doctor's global VAS score, mm	35 (23-60)	40 (26-60)	35 (19-52)	0.524
ESR, mm/h	23 (12-50)	24 (10-49)	23 (14-50)	0.628
CRP, mg/dL	0.60 (0.10-2.10)	0.40 (0.1-1.8)	0.80 (0.10-2.55)	0.110
RF, IU/mL	47 (18-112)	73 (21-231)	43 (11-99)	0.040*
RF, positive (%)	49 (75%)	26 (93%)	23 (62%)	0.003*
ACPA, U/mL	88 (22-244)	117 (22-248)	67 (25-213)	0.367
ACPA, positive (%)	57 (87%)	26 (93%)	31 (84%)	0.172
MMP-3, ng/mL	128 (67-214)	93 (62-171)	142 (70-249)	0.161
DAS28-ESR	4.27 (3.35-5.19)	4.31 (3.52-5.25)	4.27 (3.19-4.89)	0.521
J-HAQ	0.40 (0.05-0.84)	0.25 (0.04-0.71)	0.48(0.21-0.88)	0.223
MTX use, n (%)	43 (66%)	22 (79%)	21 (57%)	0.066
Dose of MTX, mg/week	8.0 (0.0-10.0)	8.0 (6.0-10.0)	5.0 (0.0-8.5)	0.046*
PSL use, n (%)	42(65%)	16 (57%)	26 (70%)	0.299
Dose of PSL, mg/day	3.0 (0.0-5.0)	2.3 (0.0-5.0)	3.0 (0.0-5.0)	0.299
Steinbrocker Stage (I, II, III, IV)	4:10:17:34	3:5:6:14	1:5:11:20	0.507
Steinbrocker Class (1, 2, 3, 4)	1:35:27:2	1:20:7:0	0:15:20:2	0.030*
Initial dose of GLM (50 mg:100 mg)	38:27	24:4	14:23	<0.001**
Number of patients with dose escalation, n (%)	20 (31%)	13 (46%)	7 (19%)	0.017*
Number of patients who discontinued treatment, n (%)	17 (26%)	6 (21%)	11 (30%)	0.450

P value was calculated by comparing naïve and switch groups. A chi-square test was used for comparison of categorical data between the two groups. The Mann-Whitney U test was used to assess continuous variables of non-paired data. *: p<0.05, **: p<0.01. Median (range).

RA: rheumatoid arthritis, VAS: visual analog scale, ESR: erythrocyte sedimentation rate, CRP: the serum C-reactive protein, RF: rheumatoid factor (positive ≥15), ACPA: anti-cyclic citrullinated peptide antibody (positive ≥4.5), MMP-3: matrix metalloprotease, DAS28-ESR: disease activity score 28-erythrocyte sedimentation rate, J-HAQ: Japanese version of the health assessment questionnaire, MTX: methotrexate, PSL: prednisolone, Steinbrocker Stage: Classification of the structural state of rheumatoid arthritis (I, II, III, IV), Steinbrocker Class: Classification of the functional state of rheumatoid arthritis (1, 2, 3, 4), GLM: golimumab

software program (SAS Institute, Cary, USA). The chi-square test was used for comparisons between two groups for categorical data, while Wilcoxon's signed rank test was used for continuous variables of paired data. In the comparison of continuous variables (baseline vs. 52 weeks and at final follow-up), 13 patients who discontinued GLM treatment before 52 weeks were excluded. The continuous variables at 52 weeks and at the final follow-up were compared with those at baseline by Wilcoxon's signed rank test adjusted using the Holm method. Regarding the Holm method, first, the p values at 52 weeks and at the final follow-up were compared. If the lower of these p values was <0.025 (0.05/2), the difference was considered significant. If the lower of these p values was ≥0.025, then both p values were considered not significant. If the higher of these p value was < 0.05, the difference was considered significant. A one-sided Wilcoxon's signed rank test was performed to evaluate the reduction in the DAS28-ESR, J-HAQ, MTX dose, and PSL dose. In addition, Wilcoxon's signed rank test was performed to evaluate the improvement in the grip power. Spearman correlation analysis was performed to determine the correlation of grip power value, J-HAQ, and DAS28-ESR at the baseline, 52 weeks, and the final follow-up. The Mann-Whitney U test was used to assess continuous variables of non-paired data. To compare the drug continuation rate between both groups, a log-rank test with the Kaplan-Meier method was used. The last observation carried forward (LOCF) method was used for missing data (29).

Results

Patients' characteristics

Sixty-five patients (58 women and 7 men) were included in the present study (Table 1). The median (range) age of patients was 69 (61-74) years old, and the median disease duration was 9 (5-16) years. Among the 65 patients, 28 were biologic-naïve (naïve group), and 37 had switched from biologics (switch group). The median (range) follow-up period was 134 (58-162) weeks. MTX was administered in 66% (43/65) of patients at a median (range) dose of 8.0 (0.0-10.0) mg/week. PSL was administered to 65% (42/65)

Table 2.   The Clinical Course of Golimumab.

		Week 0	Week 52		Final follow-up	
		Median (range)	Median (range)	p value	Median (range)	p value
DAS28-ESR	Naïve	4.31 (3.52-5.25)	2.76 (2.23-4.05)	<0.001*	2.65 (2.28-3.77)	<0.001*
	Switch	4.27 (3.19-4.89)	2.69 (2.19-3.78)	0.001*	2.89 (2.49-3.88)	0.006*
	Total	4.27 (3.35-4.27)	2.73 (2.22-3.90)	<0.001*	2.73 (2.35-3.77)	<0.001*
J-HAQ	Naïve	0.25 (0.04-0.71)	0.25 (0.05-1.03)	0.593	0.23 (0.04-0.80)	0.771
	Switch	0.48 (0.25-0.85)	0.53 (0.23-0.88)	0.490	0.53 (0.10-0.85)	0.608
	Total	0.40 (0.05-0.84)	0.40 (0.07-0.93)	0.552	0.30 (0.10-0.84)	0.761
Grip power, mmHg	Naïve	138 (104-183)	160 (102-231)	<0.001*	183 (100-234)	0.041*
	Switch	127 (93-168)	158 (112-195)	0.026*	154 (115-190)	<0.001*
	Total	133 (96-179)	158 (107-204)	<0.001*	165(105-208)	<0.001*
Dose of MTX, mg/week	Naïve	8.0 (6.0-10.0)	8.0 (3.0-8.5)	0.006*	5.0 (0.0-8.0)	<0.001*
	Switch	5.0 (0.0-8.5)	6.0 (0.0-9.0)	0.091	6.0 (0.0-8.0)	0.007*
	Total	8.0 (0.0-10.0)	7.0 (1.3-8.8)	0.003*	5.5 (0.0-8.0)	<0.001*
Dose of PSL, mg/day	Naïve	2.3 (0.0-5.0)	2.0 (0.0-5.0)	0.110	2.0 (0.0-3.8)	0.016*
	Switch	3.0 (0.0-5.0)	3.0 (0.0-5.0)	0.040	2.5 (0.0-4.0)	0.004*
	Total	3.0 (0.0-5.0)	3.0 (0.0-5.0)	0.016*	2.3 (0.0-4.0)	<0.001*

At 52 weeks and at the final follow-up, each parameter was compared with the baseline value using the Wilcoxon rank sum test adjusted by the Holm method. *: significant difference. Median (range).

DAS28-ESR: disease activity score 28-erythrocyte sedimentation rate, J-HAQ: Japanese version of the health assessment questionnaire, MTX: methotrexate, PSL: prednisolone

of patients at a median (range) dose of 3.0 (0.0-5.0) mg/day.

Other conventional DMARDs (csDMARDs) were used as follows: salazosulfapyridine in 23 cases (naïve/switch=14/9), mizoribine in 19 cases (5/14), bucillamine in 9 cases (3/6), tacrolimus hydrate in 5 cases (1/4), iguratimod in 4 cases (2/2), and actarit in 4 cases (1/3). In the switch group, 31 patients received GLM as the second bDMARD, 5 patients received it as the third bDMARD, and 1 received it as the fifth bDMARD. Moreover, patients in the switch group received infliximab (IFX) (as the first and second bDMARDs: 18, 1 case), etanercept (ETN) (as the first and second bDMARDs: 13, 3 cases), tocilizumab (TCZ) (as the first and third bDMARD: 4, 1 case), abatacept (ABT) (as the first and fourth bDMARD: 1, 1 case), and adalimumab (ADA) (as first and second bDMARD: 1, 2 cases).

There was no significant difference in the baseline status between the naïve and switch groups except for with regard to the rheumatoid factor, MTX dose, Steinbrocker Class, and initial dose of GLM (Table 1) (30). Twenty-four patients in the naïve group received 50 mg GLM; the dose was increased to 100 mg in 13 patients. Fourteen patients in the switch group received 50 mg GLM; the dose was increased to 100 mg in 7 patients. The proportion of patients who were administered 100 mg GLM as the initial dose was higher in the switch group (23/37; 62%) than in the naïve group (4/28; 14%; p<0.001).

Efficacy results

The median (range) DAS28-ESR value was 4.31 (3.52-5.25) in the naïve group and 4.27 (3.19-4.89) in the switch group at baseline (Table 2). At the final follow-up, the median (range) DAS28-ESR value had improved to 2.65 (2.28-3.77) in the naïve group and 2.89 (2.49-3.88) in the switch

group. The J-HAQ did not improve in either group. The ratio of low disease activity and remission improved from naïve 18% (5/28)/switch 24% (9/37) at baseline to naïve 60% (15/25)/switch 52% (14/27) at 52 weeks (p<0.05) and naïve 64% (16/25)/switch 67% (18/27) at the final follow-up (p<0.01) (Fig. 1). The median grip power at 52 weeks and at the final follow-up improved in both groups. The MTX and PSL doses were decreased at the final follow-up. The Spearman correlation coefficients of the grip power, J-HAQ, and DAS28-ESR were ρ=-0.426 (grip power vs. J-HAQ), ρ=-0.417 (grip power vs. DAS28-ESR), and ρ=0.348 (J-HAQ vs. DAS28-ESR) (p<0.001).

Continuation rate and reason for discontinuation

The continuation rate at the final follow-up [median (range): 134 (58-162) weeks] was 22/28 (78.6%) in the naïve group and 26/37 (70.3%) in the switch group. The respective continuation rates of the naïve/switch/total groups calculated using the Kaplan-Meier method were 89.3%/73.0%/80.0% at 52 weeks, 81.1%/73.0%/76.4% at 104 weeks, and 76.3%/68.7%/71.6% at 156 weeks (Fig. 2). No significant difference was detected in the continuation rate between the naïve and switch groups (p=0.829). The continuation rate in patients who were administered MTX was higher than that in patients who were not administered MTX (p=0.001; Fig. 3). On comparing the backgrounds of the naïve and switch groups, patients without MTX had higher median (range) values for the age, C-reactive protein (CRP), ESR, matrix metalloprotease-3 (MMP-3), and rheumatoid factor (RF) at baseline than those with MTX (p<0.05) [patients without MTX vs. patients with MTX, age 73 (69-78) vs. 65 (54-70), CRP 1.65 (0.25-3.23) vs. 0.40 (0.10-1.50), ESR 45 (23-80) vs. 18 (10-28), MMP-3 171 (87-367) vs. 95
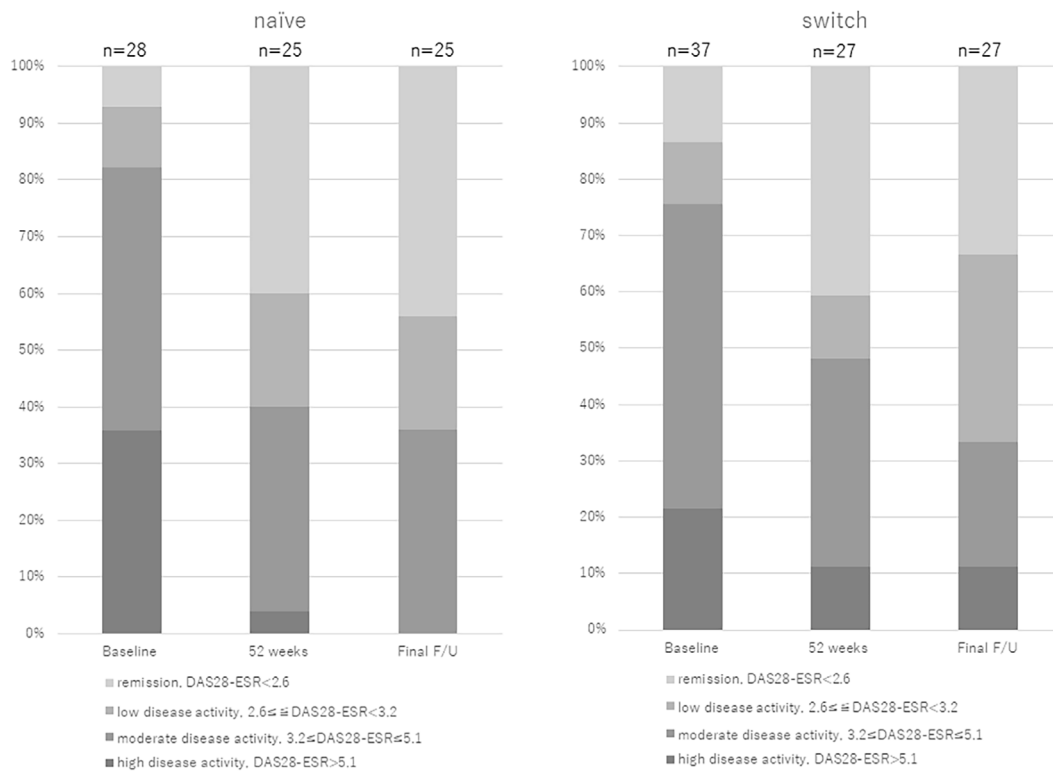
Figure 1. The DAS28-ESR at baseline, 52 weeks, and the final follow-up. The DAS28-ESR classification improved from baseline to 52 weeks and at the final follow-up in both groups (chi-square test: p<0.05). The classification of DAS28-ESR was as follows: remission, DAS28-ESR<2.6; low disease activity, 2.6≤DAS28-ESR<3.2; moderate disease activity, 3.2≤DAS28-ESR≤5.1; high disease activity, DAS28-ESR>5.1. DAS28-ESR: disease activity score 28-erythrocyte sedimentation rate
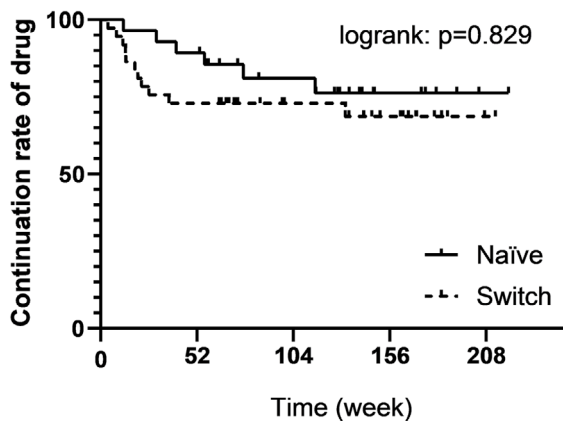
Number of patients at risk

	52W	104W	156W
Naïve	25	17	6
Switch	27	17	11

Figure 2. Drug continuation rates in the naïve and switch groups. The drug continuation rate showed no significant difference between both groups (log rank: p=0.829).
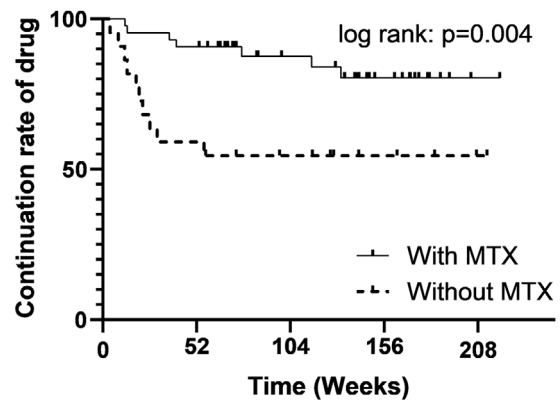
Number of patients at risk

	52W	104W	156W
With MTX	39	25	12
Without MTX	13	9	5

Figure 3. Drug continuation rates in groups administered GLM with and without MTX. The group administered GLM with MTX showed a better drug continuation rate than the group administered GLM without MTX (log rank: p=0.004). GLM: golimumab, MTX: methotrexate

(60-194), RF 83 (33-162) vs. 23 (13-106)]. Seventeen patients discontinued the administration of GLM. The reasons for discontinuation were as follows: lack of efficacy (8/65:

12.3%), infection (3/65: 4.6%), and eczema, multiple sclerosis, economic reasons, patient preference for bDMARDs, fracture, and transfer to another hospital in 1 case each (1/

65: 1.5%). Ten patients (1 naïve, 9 switch) discontinued GLM within 26 weeks, and 3 discontinued GLM between 26 and 52 weeks. Five patients discontinued GLM within 26 weeks because of a lack of efficacy. No patients discontinued GLM due to remission.

Discussion

In this study, evaluated the effectiveness and continuation rate of GLM for long-term use in daily practice for patients with RA. We recorded the clinical effect and the continuation rate of GLM in daily practice after 52 weeks. As hypothesized, GLM showed effectiveness not only in bDMARD-naïve patients but also in switch patients. In our institution, 38 patients started GLM 50 mg; however, 20 increased the dose to 100 mg because the 50-mg regimen was inadequate. Increasing the dose improved the DAS; therefore, if the 50-mg regimen is not effective, increasing the dose should be considered. The GO-AFTER study has also reported the clinical efficacy of switching to GLM therapy (14). In agreement with this finding, we found that GLM therapy was effective even for the switch group patients.

The remission rate of the naïve/switch group was 40% (10/25)/41% (11/27) at 52 weeks and 44% (11/25)/33% (9/27) at the final follow-up. In the GO-FORTH and GO-FORWARD trials, the rates of remission based on the DAS 28-ESR were 32.4-52.2% at 52 weeks, 39.4-75.8% at 104 weeks, and 55.3-61.8% at 156 weeks (2, 5). In 2 previous studies, the average age at the baseline was 50 years old, and the average DAS28-ESR at the baseline was 5.5-5.9; these patients showed better remission rates at 52 and 104 weeks than did our patients (2, 5). In our trial, the median age of the recruited patients was 69 years old. Thus, the age and age-related complications might have affected the remission rate in our patients. In the GO-AFTER trial, the remission rate of the bDMARD switch group for 52/100/160 weeks was 12.5-15.6% for the 50 mg regimen and 21.5-22.1% for the 100 mg regimen (3). The switch group in our study showed a better remission rate than that in the GO-AFTER study. The higher the remission rate of the switch group in our study may have been due to the better DAS28-ESR at baseline than in the GO-AFTER study. In the present study, we recruited older patients than those described in previous studies (16, 31, 32), and we therefore believe that the 65 patients that were collected from a single institution with 134 (58-162) weeks of follow-up thus provided valuable information in comparison to previous studies.

The J-HAQ was not improved at the final follow-up compared with that at the baseline in the present study, which was inconsistent with our hypothesis. The HAQ score in healthy populations was reported to be 0.49 (33). The GO-FORWARD, GO-FORTH, GO-AFTER, and GO-MONO trials reported improvements in the HAQ-DI (0.37-0.75), and the HAQ-DI baseline values ranged from 0.9 to 1.6 (6, 31, 32, 34). In these 4 clinical trials, the mean age

ranged from 50-55 years old, and the mean DAS28-ESR ranged from 5.5-6.3. The age and DAS28-ESR were higher in our study than in those previous trials. Furthermore, in our study, 17/65 (26%) patients were classified as Steinbrocker stage III and 34/65 (52%) as Steinbrocker stage IV. Despite the low J-HAQ score (0.40) of our case series at the baseline, the number of patients in the different Steinbrocker classes were as follows: 1 in class 1, 35 in class 2, 27 in class 3, and 2 in class 4. The Steinbrocker Stage and Class in our study indicated that most patients had some irreversible ADL impairments. Furthermore, in the present study, the grip power was correlated with the J-HAQ score (ρ= -0.426, p<0.01) and DAS28-ESR (ρ=-0.417, p<0.01). Therefore, we consider it necessary to evaluate the grip power when assessing subclinical joint dysfunction.

Consistent with our hypothesis, in the present study, treatment with GLM improved the grip power at 52 weeks and at the final follow-up. The use of GLM not only suppressed joint inflammation but also improved the grip power. Uutela et al. (35) reported that the grip power reflected the disease status, such as remission, low/moderate disease activity, and high disease activity. The present study showed that the grip power was correlated with the J-HAQ and DAS28-ESR as continuous variables. Eberhardt et al. reported that the use of TNF inhibitors for more than one year in patients with RA improved the grip power. However, details concerning the TNF inhibitors were not provided. As their study findings were published in 2007, GLM would not have been used (27). Aside from the abovementioned study by Eberhardt et al., there have been no reports showing improvements in the grip power following the use of TNF inhibitors. Our study is thus the first to show an improvement in the grip power in daily practice following GLM use. Improving the grip power may promote the prevention of sarcopenia and frailty in the future. Therefore, measuring the grip strength will likely provide supplemental information about potential ADL impairment.

Only 17 patients (26.1%) discontinued the treatment course in our study, indicating a high continuation rate for long-term GLM use. The ANSWER cohort study, comprising 2,494 patients in real clinical practice, reported the retention rates of the following 7 bDMARDs: ABT (75.5%), TCZ (71.5%), GLM (65.6%), ETN (61.2%), certolizumab pegol (60.7%), ADA (58.2%), and IFX (53.4%) at 36 months in adjusted model (36). A systematic review by Svedbom et al. reported that the continuation rate of GLM was higher than that of other TNF inhibitors (9). An important characteristic of GLM is its lower antigenicity than other bDMARDs (37). The low antibody production against GLM is likely associated with its high continuity.

Svedbom et al. showed that the respective continuation rates of GLM in real clinical practice at 52/104/156 weeks were 67-76%/49-63%/60% for bDMARD-naïve patients and 47-63%/40-61%/32-54% for bDMARD-switch patients (9). Kondo et al. reported that the continuation rate of GLM after 6 years was 50.3% (38). Compared with these data from

real clinical practice, our study findings showed a better continuation rate of GLM in both the naïve and switch groups. However, the systematic review by Svedbom et al. included abstracts from academic conferences, which may have provided inadequate information. Therefore, it would be difficult to precisely analyze the reason for the difference between our findings and those of the systematic review.

In our study, patients discontinued the treatment course due to a lack of efficacy (8/65: 12.3%), toxic effects (5/65: 7.7%), and other reasons (4/65: 6.2%). None of the patients discontinued the treatment due to remission. In the AN-SWER cohort study, the drug retention rate of GLM in the adjusted model at 36 months was as follows: lack of effectiveness (74.0%), toxic effect (89.1%), and remission (92.5%) (28). Ten patients discontinued GLM within 26 weeks, and 3 discontinued between 26 and 52 weeks. Five patients discontinued GLM because of a lack of efficacy within 26 weeks. Kondo et al. reported that the discontinuation of the treatment course frequently occurred within six months (38). A steady-state plasma concentration can be achieved with 12 weeks of repeated injection of GLM (39), which is longer than that of other TNF-inhibitors (40). The GO-FORTH trial results showed that concurrent use of MTX leads to earlier disease control at three and six months than GLM monotherapy and switching therapy [based on the American College of Rheumatology criteria (41)] for two to five years (2, 14, 16). Considering the discontinuation of drug administration within 26 weeks in the present study, we suggest that tight control of the RA status within 26 weeks is necessary until GLM exhibits effectiveness, especially in monotherapy and switching therapy groups. The continuation rate was higher in patients who were administered MTX than in those who were not. Concurrent use of MTX with GLM decreases immunogenicity and adverse events (42). The patients without MTX were older and had higher CRP, ESR, MMP-3, and RF values than the patients with MTX; therefore, older patients and those with more severe inflammation are likely to be more adversely affected by continuation of GLM. According to the EULAR recommendation (17), if MTX is not contraindicated, it should be administered. It was challenging to administer MTX to patients without MTX because of other medical complications. Our data also showed a reduction in PSL use at the final follow-up, suggesting that the use of PSL for the short term soon after GLM induction would facilitate a decrease in disease activity until GLM exhibits effectiveness up to 26 weeks. Introduction of the 100-mg GLM regimen would facilitate the early suppression of disease and prevent early drop-out from treatment.

Several limitations associated with the present study warrant mention. This was a retrospective study, and the sample size was smaller than that of clinical trials. Furthermore, the concurrent use of csDMARDs (including MTX and other csDMARDs) differed among the naïve and switch groups. The final selection and dosage of bDMARDs was decided by discussion between the patient and the doctor. The initial dose of GLM was decided while considering not only the patient's disease status but also their economic status. Our study lacks adequate data to explore the risk of discontinuation using a multivariate analysis, as 17 patients discontinued the study.

Conclusion

GLM improved the disease activity and grip power in bDMARD-naïve and switch groups. The concurrent use of MTX with GLM showed a better continuation rate than GLM administration without MTX. This is the first report to show the improvement in the grip power by GLM and to demonstrate that the use of GLM can prevent sarcopenia in the future. We also found that the grip power was correlated with the J-HAQ and DAS28-ESR. Our findings concerning the effects of GLM may facilitate further studies on effective RA treatment regimens.

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