



Effect of Golimumab Dose Escalation in Japanese Patients With Rheumatoid Arthritis: Post-Hoc Analysis of Post-Marketing Surveillance Data

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ABSTRACT

Introduction: While dose escalation of golimumab has been used for patients with rheumatoid arthritis who demonstrate an inadequate response to the standard dose, its effectiveness has not been fully evaluated. The aim of this study was to assess the clinical outcome observed by dose escalation of golimumab for patients with rheumatoid arthritis in the daily clinical setting.

Methods: A post hoc analysis was performed of data from the 24-week post-marketing

surveillance conducted in Japan ($n = 5154$). A total of 301 patients with moderate or high disease activity at baseline who underwent dose escalation of golimumab were assessed for effectiveness at 24 weeks based on several variables, such as DAS28-CRP, SDAI, and CDAI, as well as for medication persistence through 24 weeks. In addition, the study population was stratified by the time to dose escalation, and effectiveness was likewise evaluated. Logistic regression analysis was performed to identify factors associated with a moderate/good EULAR response to golimumab at 24 weeks.

Results: Patients with golimumab dose escalation showed significant improvement of the clinical signs and symptoms of rheumatoid arthritis at 24 weeks, as indicated by reduction of the DAS28-CRP ($\Delta 0.89$), SDAI ($\Delta 8.64$), and CDAI ($\Delta 8.28$) scores. This result was relatively consistent across the subgroups stratified by the timing of dose escalation. According to Kaplan-Meier analysis, 78.1% of the patients continued to receive golimumab at 24 weeks, and this was also similar among the subgroups stratified by the time to dose escalation. Multivariate analysis identified male sex and previous biologic therapy as factors that were significantly associated with the clinical response at 24 weeks.

Conclusion: In real-world clinical practice, improvement of disease activity was observed after uptitration of golimumab from 50 to 100 mg regardless of the timing. Male patients

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and biologic-naive patients were more likely to respond to dose escalation of golimumab.

Trial Registration: UMIN-CTR, Identifier: UMIN000015895.

Keywords: Dose escalation; Golimumab; Post-marketing surveillance; Real-world evidence; Rheumatoid arthritis

Key Summary Points

Why carry out this study?

Golimumab (GLM), a fully human monoclonal antibody targeting TNF, is approved at 50 mg or 100 mg every 4 weeks for the treatment of rheumatoid arthritis (RA) in Japan

In real-world practice, dose escalation of GLM from 50 to 100 mg seems to achieve better control in RA patients with higher disease activity, but there have been only few reports supporting a clinical benefit of this strategy

The aim of this study is to assess the clinical outcome of GLM dose escalation in a real-world clinical practice using the data from post-marketing surveillance of GLM conducted in Japan

What was learned from the study?

In a real-world clinical setting, improvement of disease activity was observed after uptitration of golimumab from 50 to 100 mg regardless of the timing

Male patients and biologic-naive patients were more likely to respond to dose escalation of golimumab, but further investigation will be required to identify useful predictors at the time of dose escalation

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic debilitating systemic inflammatory disease that leads to joint destruction and functional disability. It is estimated that up to 1% of the Japanese population has RA [1]. The strategy for management of RA has been improved considerably since the introduction of biologic agents targeting key molecules implicated in the pathogenesis of this disease. Tumor necrosis factor (TNF) inhibitors were among the first biologic agents proven to be effective for suppression of disease activity and progression of joint damage [2].

Golimumab (GLM), a fully human monoclonal antibody targeting TNF, has been demonstrated to be an effective treatment for RA [3–7]. In Japan, subcutaneous GLM (50 mg or 100 mg every 4 weeks) is approved for adults with moderate to severe RA. In the phase 3 GO-FORTH study conducted in Japan, clinical efficacy was comparable between the two doses of GLM, but inhibition of radiographic progression was numerically better in patients treated with 100 mg of GLM + methotrexate (MTX) than in patients receiving 50 mg of GLM + MTX [4]. The GO-FORTH study was not designed to compare GLM dosages, but post hoc analysis suggested that a GLM dose of 100 mg was more likely to be effective than 50 mg for preventing structural damage in patients with high disease activity and patients with high CRP levels [8]. There have been few reports supporting a clinical benefit of GLM dose escalation. In the GO-FORTH study, 9 out of 86 subjects who initiated GLM at a dose of 50 mg underwent dose escalation to 100 mg as rescue treatment because of lack of efficacy, resulting in subsequent improvement of the signs and symptoms of RA [4]. In real-world daily practice, dose escalation of GLM seems to achieve better control in RA patients with higher disease activity [9]. However, dose escalation of biologic agents needs to be carefully appraised since this approach can lead to higher medical costs [10] that impose a greater burden on the healthcare system.

Therefore, the present study was designed to assess the clinical effect of GLM dose escalation

in real-world clinical practice. We analyzed data from post-marketing surveillance (PMS) of GLM conducted in Japan, focusing on the population of patients who underwent dose escalation during the 24-week study period.

METHODS

Study Design and Patients

As described previously [11], 5154 patients with RA who were treated with golimumab (GLM) in Japan between September 2011 and May 2013 were monitored for 24 weeks at selected medical facilities across Japan. The enrolled patients received subcutaneous GLM (50 mg or 100 mg) once every 4 weeks, with dose escalation (from 50 to 100 mg) or reduction (from 100 to 50 mg) at the discretion of the treating physician. Patients who underwent dose escalation of GLM were included in this study if they had moderate or high disease activity according to the DAS28-CRP score at study entry. Patients who underwent dose escalation of GLM multiple times and patients who started GLM at 100 mg were excluded.

This article is based on previously conducted PMS study and does not contain any new interventional studies with human participants or animal subjects performed by any of the authors. The PMS study protocol and ethical considerations were assessed by the internal review board members and approved by the Japanese PMDA. This PMS study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, Identifier: UMIN000015895), was conducted in accordance with the Japanese regulations (Ministry of Health, Labor, and Welfare Ministerial Ordinance No. 171) on Good Post-marketing Study Practice (GPSP), and was carried out by Janssen Pharmaceutical K.K. after a contract with each study center.

Assessment of Effectiveness

The effectiveness of GLM was assessed by analyzing changes of the Disease Activity Score 28

based on C-reactive protein (DAS28-CRP), the Clinical Disease Activity Index (CDAI), and the Simplified Disease Activity Index (SDAI) at 24 weeks from baseline. The EULAR response was also evaluated from the absolute change of DAS28-CRP as well as the remission rates based on DAS28-CRP, CDAI, and SDAI scores at 24 weeks. Cutoff values for disease activity (high/moderate/low) were defined for the DAS28-CRP (5.1/3.2/2.6), SDAI (26/11/3.3), and CDAI (22/10/2.8) scores. Remission was defined as DAS28-CRP \leq 2.6, SDAI \leq 3.3, and CDAI \leq 2.8. A good EULAR response was defined as a decrease of DAS28-CRP from baseline by $>$ 1.2 if it was \leq 3.2 at 24 weeks. A moderate EULAR response was defined as a decrease of DAS28-CRP from baseline by $>$ 1.2 if the value was $>$ 3.2 at 24 weeks or a decrease of DAS28-CRP from baseline by $>$ 0.6 and \leq 1.2 if it was \leq 5.1 at 24 weeks.

Statistical Analysis

Data are presented as mean \pm standard deviation (SD) for continuous variables and as proportions (%) for categorical variables unless otherwise described. The paired *t* test was performed to compare changes of variables from baseline to week 24, and statistical significance was defined as $p < 0.05$ (two-tailed). *P* values were adjusted for multiplicity by the Bonferroni method. Kaplan-Meier analysis was conducted to estimate treatment persistence, which was defined as the period from initiation of GLM to its discontinuation for any reason. Survival curves were compared with the log-rank test, using the subgroup who underwent dose escalation at 4 weeks as a reference, and log-rank *p* values were corrected for multiple comparisons by the Bonferroni method.

Univariate logistic regression analysis was performed to examine the association between patient characteristics and a good or moderate EULAR response, followed by multivariate logistic regression analysis. Variables tested in the univariate logistic regression analysis were also evaluated in multivariate models. In all analyses, $p < 0.05$ was considered statistically significant. Associations were assessed by

calculating the odds ratio (OR) with 95% confidence interval (CI).

Effectiveness was assessed in the modified intent-to-treat (ITT) population, which included patients who at least had baseline data. If the 24-week data were missing, baseline values were carried forward for imputation. Effectiveness was also assessed in the observed case (OC) population, which included patients who had data at both baseline and 24 weeks, as a sensitivity analysis to confirm the robustness of results obtained by ITT analysis.

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Disposition and Baseline Characteristics

As reported previously, a total of 5154 patients were enrolled in the post-marketing surveillance (PMS) of golimumab (GLM), and 5137 patients were included in the safety analysis set, of which 4331 started GLM at 50 mg every 4 weeks [11]. Among these patients, 301 had high or moderate disease activity at study entry and underwent one dose escalation (to 100 mg every 4 weeks) during the 24-week treatment, fulfilling the study criteria for the ITT effectiveness analysis population (Fig. 1). In this population, dose escalation was more frequent at earlier time points (week 4, $n = 85$; week 8, $n = 63$; week 12, $n = 62$; week 16, $n = 44$; week 20, $n = 47$). The patients showed female predominance (81.7%). The mean age was 62.3 ± 13.4 years, and the mean disease duration was 10.4 ± 10.0 years. The mean disease activity scores were as follows: DAS28-ESR, 5.48 ± 1.10 ; DAS28-CRP, 4.81 ± 0.99 ; SDAI, 28.59 ± 12.14 ; CDAI, 26.18 ± 11.60 . Approximately two-thirds of the patients (64.5%) had previously used biologic disease-modifying antirheumatic drugs (bDMARDs), and the majority were on concomitant glucocorticoids (62.2%, mean dose: 5.01 ± 3.13 mg) and MTX (78.8%, mean dose: 8.97 ± 3.61 mg) during the study period (Table 1). When stratified by the time to dose escalation (4, 8, 12, 16, or

20 weeks), overall demographic and baseline characteristics were generally comparable across all subgroups. However, the patients who underwent dose escalation at 8 weeks showed harder-to-treat baseline characteristics such as a higher frequency of comorbidities (82.5% vs. 75.7% in the total effectiveness population) and previous bDMARD exposure (79.4% vs. 64.5% in the total effectiveness population; Table 1).

Persistence with GLM Stratified by the Time to Dose Escalation

Kaplan-Meier analysis revealed that persistence (i.e., average time to discontinuation) with GLM after dose escalation was as follows in each subgroup: week 4, 19.7 weeks; week 8, 20.3 weeks; week 12, 21.6 weeks; week 16, 22.7 weeks; week 20, 23.5 weeks. When the week 4 subgroup was compared with the other subgroups, only the week 20 subgroup was significantly different (log-rank $p = 0.005$), presumably because of the short follow-up period after dose escalation (Fig. 2). Overall, 21.9% of patients discontinued GLM treatment after dose escalation, and the primary reason was the progression of disease in all the subgroups (Supplementary Table 1).

Effectiveness of GLM Stratified by the Time to Dose Escalation

The mean DAS28-CRP of the total study population improved significantly from 4.81 to 3.92 at 24 weeks ($p < 0.001$). Similarly, subgroup analyses demonstrated a significant decrease of DAS28-CRP regardless of the timing of dose escalation (Fig. 3a: $p < 0.001$ with Bonferroni correction). Pairwise comparisons between subgroups failed to detect statistically significant differences for any combinations (Supplementary Table 2). Likewise, significant reduction of the CDAI and SDAI scores from baseline was observed in the overall study population (Fig. 3b, c: both $p < 0.001$). This was also true when stratified by the timing of dose escalation, with no significant differences among the subgroups being detected by pairwise comparisons (Supplementary Table 2).

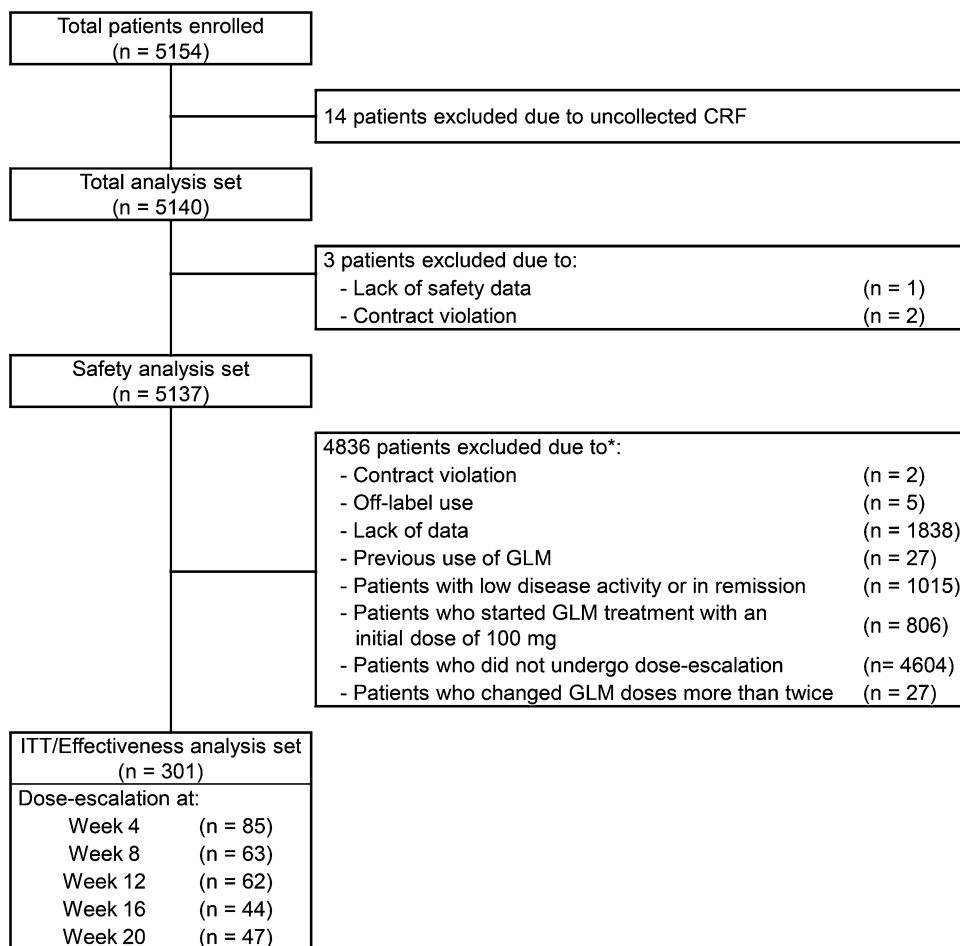


Fig. 1 Flow diagram of patient disposition demonstrating the number of patients included in each population of the present study. *ITT* intent to treat, *GLM* golimumab.

*Patients could be allocated to more than one category for exclusion criteria

Overall, 46.1% of patients who underwent dose escalation achieved a good (24.4%) or moderate (21.7%) EULAR response at 24 weeks. Consistent with this result, approximately 50% of the patients in each dose escalation subgroup demonstrated a good or moderate EULAR response (Fig. 4a), with no statistical differences among the subgroups (Supplementary Table 3). Remission based on DAS28, SDAI, and CDAI was observed in 23.2%, 9.5%, and 9.1% of the overall study population, respectively (Fig. 4b), increasing to 30.8%, 27.7%, and 32.1%, respectively, when patients with low disease activity were included (Fig. 4c). Although numerical differences were observed, we did not detect any significant inter-subgroup

differences (Supplementary Table 3). Across the overall effectiveness analysis, the week 8 subgroup tended to show less improvement, which was possibly related to its baseline characteristics. Overall, patients who received GLM dose escalation from 50 to 100 mg demonstrated significant improvement of their signs and symptoms irrespective of the timing of dose escalation. This conclusion was strengthened by the sensitivity analysis in the OC population, which revealed similar trends for all variables assessed (Supplementary Table 4).

Logistic regression analysis suggested that the likelihood of achieving a moderate or good EULAR response at 24 weeks was significantly higher in males ($p = 0.015$) and in biologic-

Table 1 Baseline demographics and clinical characteristics of the efficacy analysis set

	Total <i>n</i> = 301	GLM dose escalated at:				
		4 weeks <i>n</i> = 85	8 weeks <i>n</i> = 63	12 weeks <i>n</i> = 62	16 weeks <i>n</i> = 44	20 weeks <i>n</i> = 47
Sex						
Male/female, %	18.3/81.7	14.1/85.9	19.0/81.0	14.5/85.5	22.7/77.3	25.5/74.5
Age (years)	62.3 ± 13.4	62.0 ± 14.4	61.7 ± 12.7	62.5 ± 13.8	61.7 ± 13.6	64.3 ± 12.3
Duration of RA (years)	10.4 ± 10.0	10.6 ± 9.7	10.1 ± 11.3	10.8 ± 9.4	10.0 ± 10.0	10.6 ± 10.1
Tender joint count (0–68)	7.9 ± 6.4	7.5 ± 6.7	8.0 ± 5.7	9.0 ± 7.0	7.4 ± 6.5	7.3 ± 5.8
Swollen joint count (0–66)	6.3 ± 5.2	6.8 ± 5.3	5.5 ± 5.0	6.9 ± 5.8	5.7 ± 4.3	5.9 ± 5.3
ESR (mm/h)	48.37 ± 31.64	50.89 ± 34.00	50.57 ± 33.04	48.50 ± 30.74	40.69 ± 27.38	49.31 ± 31.65
CRP (mg/dl)	2.28 ± 2.60	2.11 ± 2.21	2.29 ± 2.91	2.78 ± 2.86	2.35 ± 3.07	1.85 ± 1.91
Patient VAS	62.07 ± 22.29	61.46 ± 21.63	64.22 ± 23.17	62.52 ± 23.65	64.25 ± 23.40	57.66 ± 19.43
Physician VAS	55.05 ± 20.77	57.15 ± 21.41	53.14 ± 21.69	55.91 ± 22.19	54.60 ± 18.85	53.17 ± 18.85
DAS28-ESR	5.48 ± 1.10	5.58 ± 1.10	5.52 ± 1.10	5.61 ± 1.29	5.30 ± 1.01	5.28 ± 0.88
DAS28-CRP	4.81 ± 0.99	4.84 ± 1.02	4.75 ± 0.98	5.01 ± 1.11	4.74 ± 0.98	4.63 ± 0.79
SDAI	28.59 ± 12.14	28.73 ± 12.99	28.24 ± 11.65	31.41 ± 13.63	27.66 ± 10.96	26.12 ± 9.95
CDAI	26.18 ± 11.60	26.44 ± 12.36	25.88 ± 11.19	28.51 ± 13.06	25.10 ± 10.07	24.23 ± 1.00
Disease activity (DAS28-CRP), %						
High/Moderate	36.1/63.9	35.7/64.3	36.5/63.5	40.3/59.7	37.2/62.8	29.8/70.2
Steinbrocker's stage, %						
I/II/III/IV	11.7/26.3/ 24.0/38.0	16.5/23.5/ 17.6/42.4	9.7/25.8/27.4/ 37.1	12.9/17.7/ 29.0/40.3	13.6/34.1/ 22.7/29.5	2.1/36.2/25.5/ 36.2
Steinbrocker's class, %						
I/II/III/IV	11.3/52.3/ 33.0/3.3	15.3/45.9/ 34.1/4.7	11.3/56.5/ 27.4/4.8	6.5/51.6/41.9/ 0.0	11.4/52.3/ 31.8/4.5	10.6/59.6/ 27.7/2.1
Comorbidities, %						
Hepatic dysfunction	75.7	69.4	82.5	74.2	75.0	80.9
Renal impairment	14.6	15.3	17.5	9.7	20.5	10.6
Previous biologics, %	6.6	5.9	7.9	3.2	6.8	10.6
Etanercept	64.5	65.9	79.4	67.7	52.3	48.9
Infliximab	50.0	50.0	50.0	57.1	26.1	60.9
	38.7	41.1	34.0	31.0	43.5	52.2

Table 1 continued

	Total <i>n</i> = 301	GLM dose escalated at:				
		4 weeks <i>n</i> = 85	8 weeks <i>n</i> = 63	12 weeks <i>n</i> = 62	16 weeks <i>n</i> = 44	20 weeks <i>n</i> = 47
Adalimumab	37.6	30.4	34.0	42.9	52.2	39.1
Abatacept	26.8	25.0	16.0	40.5	43.5	13.0
Tocilizumab	28.9	25.0	28.0	35.7	21.7	34.8
Previous medication, %						
Glucocorticoid	60.5	62.3	58.3	63.3	55.8	60.9
MTX	78.0	66.2	80.0	81.7	83.7	84.8
csDMARDs other than MTX	38.1	48.1	41.7	26.7	27.9	41.3
Concomitant medication during PMS						
Glucocorticoid, %	62.2	66.7	61.7	63.3	54.5	60.9
Dose (mg/day, mean)	5.01 ± 3.13	5.10 ± 3.03	4.53 ± 2.31	4.79 ± 2.77	5.91 ± 4.81	5.08 ± 2.86
MTX, %	78.8	67.9	80.0	83.3	84.1	84.8
Dose (mg/day, mean)	8.97 ± 3.61	8.57 ± 3.56	9.80 ± 3.77	8.86 ± 3.69	9.34 ± 3.50	8.29 ± 3.31
csDMARDs other than MTX, %	43.1	55.1	46.7	28.3	34.1	45.7

RA rheumatoid arthritis, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *VAS* visual analog scale, *DAS28-CRP* Disease Activity Score 28 based on C-reactive protein, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *MTX* methotrexate, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *GLM* golimumab

naïve patients ($p = 0.013$). No significant associations were identified for the other demographic and baseline clinical characteristics (Table 2).

DISCUSSION

Although GLM is approved at two dosages (i.e., 50 mg and 100 mg) for the treatment of active RA in Japan, there has been little evidence as to whether dose escalation confers additional clinical benefit for control of disease activity.

The present study demonstrated that RA patients with moderate to high disease activity who underwent GLM dose escalation significantly improved the clinical signs and symptoms as indicated by reduction of the DAS28-CRP, CDAI, and SDAI scores. When effectiveness was assessed by the EULAR response, about half of the patients exhibited a good or moderate response after dose escalation. In addition, approximately 30% improved to show low disease activity or remission after dose escalation. We also demonstrated that the clinical response

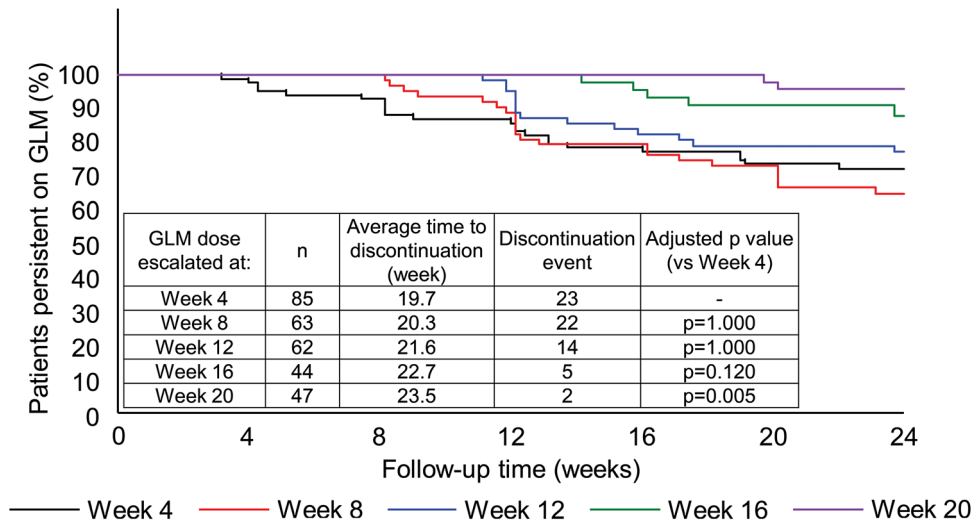


Fig. 2 Persistence with GLM treatment stratified by the timing of dose escalation. Kaplan-Meier analysis was performed to assess persistence with GLM treatment based on the time when the GLM dose was increased from 50 to 100 mg during the observation period of the

24-week post-marketing surveillance. Each of the Kaplan-Meier curves was compared with the week 4 curve by the log-rank test, and the *p* values were adjusted for multiple comparisons by using Bonferroni correction. Descriptive statistics are shown in the table. *GLM* golimumab

at 24 weeks was similar regardless of the time to dose escalation of GLM, suggesting that emergence of the response was prompt and a plateau occurred within 4 weeks.

The effect of dose escalation observed in the current study of a real-world patient population is consistent with the results of the GO-FORTH randomized clinical trial conducted in Japanese RA patients with an inadequate response to MTX. In that study, nine patients received rescue treatment by GLM dose escalation from 50 to 100 mg due to lack of efficacy and demonstrated improvement of the ACR20 response rate [4]. Here, we found that the patients who underwent dose escalation of GLM demonstrated improvement of disease activity at 24 weeks. Since the current study only included patients with moderate or high disease activity at study entry, it is speculated that this population was likely to undergo dose escalation due to insufficient response to GLM at a dose of 50 mg. Our results therefore suggest that poor responders to 50 mg of GLM may be benefited from uptitration of GLM to 100 mg in controlling disease activity. On the other hand, a previous post hoc analysis of the GO-FORTH study, which suggested that initiating GLM therapy at

100 mg might be more beneficial than initiating at 50 mg for preventing joint destruction in patients with high disease activity or a high CRP [8]. Currently, there is no evidence directly comparing the efficacy between initiating GLM at 100 mg versus increasing the dose of GLM to 100 mg. Yet, given the fact that patients and physicians are required to consider economic implications when selecting treatment strategies, it would be valuable to provide more therapeutic options as suggested by the data presented in the current study. However, it should be noted that the current study did not analyze patient characteristics at the time of dose escalation because the PMS protocol did not require clinical evaluation at time points other than weeks 0 and 24. Thus, while our data clearly indicate the clinical effect of starting GLM at 50 mg and increasing the dose to 100 mg as needed, the net benefit of dose escalation itself cannot be determined.

The clinical benefit of dose escalation of biologic agents for RA has been best studied with infliximab, which is indicated for dose escalation or dose intensification if the response is insufficient. Previous studies have demonstrated that patients with an inadequate

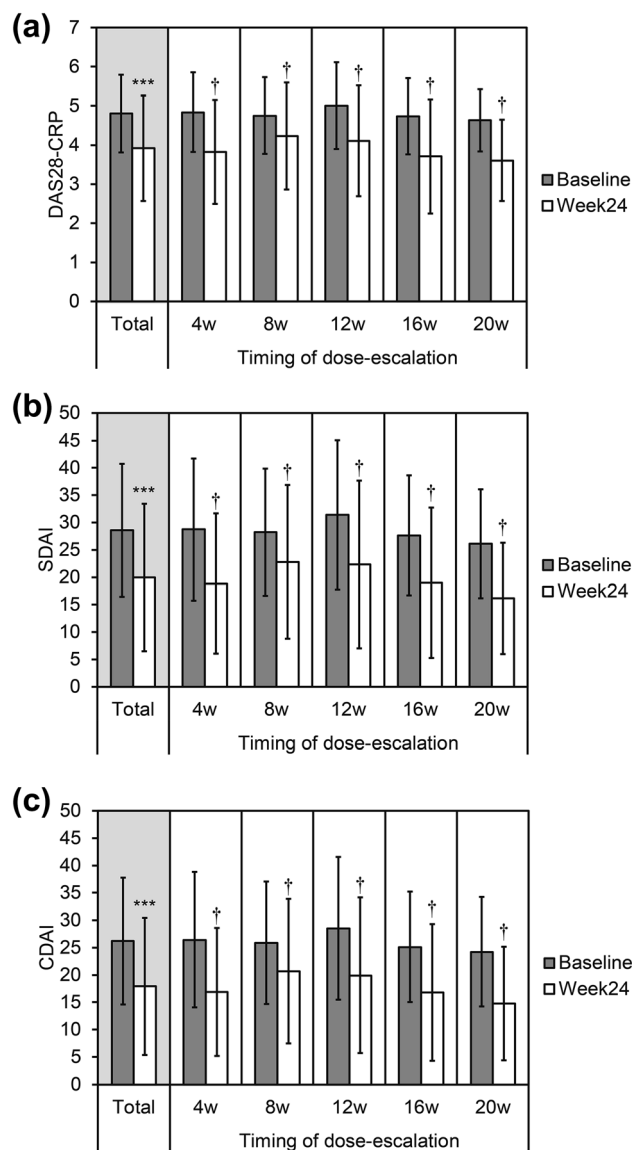
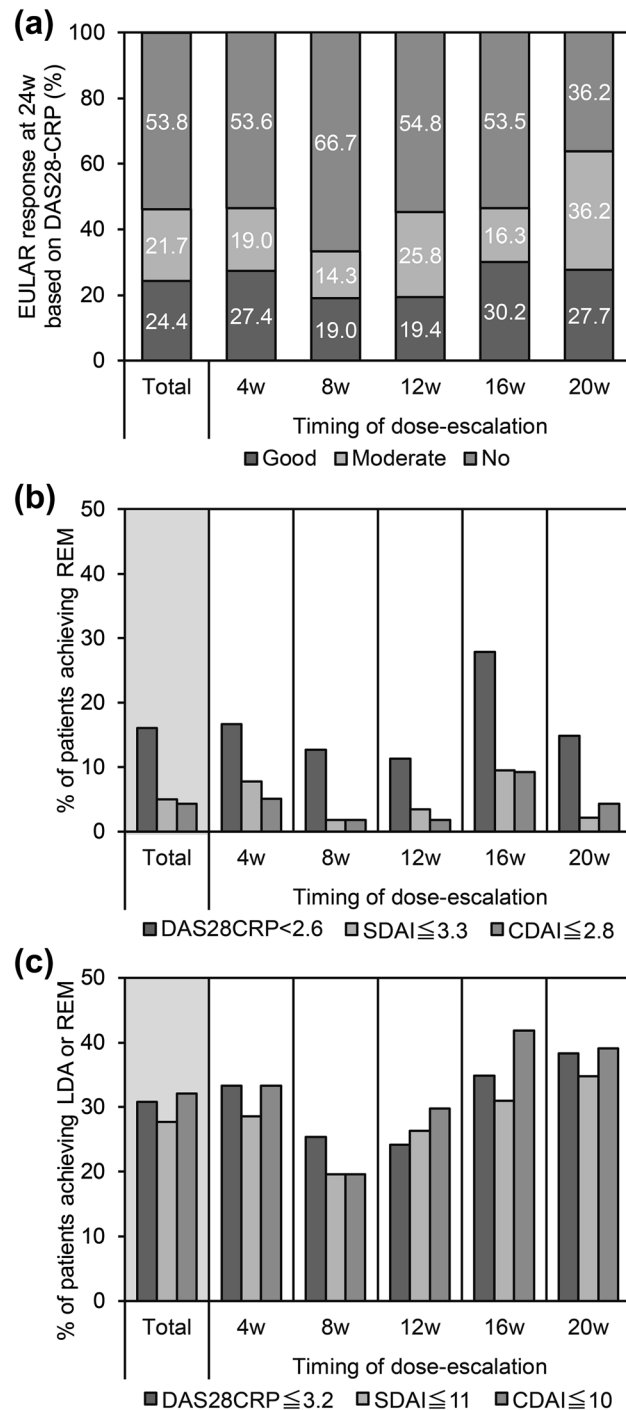


Fig. 3 Disease activity at baseline and week 24 in patients on GLM treatment. For each subgroup stratified by the timing of dose escalation, disease activity at baseline (0 week) and 24 weeks was evaluated from the DAS28-CRP (a), CDAI (b), or SDAI (c) score. *DAS28-CRP*, Disease Activity Score 28 based on C-reactive protein, *CDAI*

Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *GLM* golimumab. *** $p < 0.001$ versus baseline by the paired t -test. † $p < 0.0001$ versus baseline by the paired t -test with Bonferroni correction for multiplicity

response to infliximab at a starting dose of 3 mg/kg generally had a low trough serum concentration [12–14]. Immunogenicity is strongly associated with low serum concentrations of infliximab and subsequent attenuation of the clinical response [15–18]. It has previously been suggested that dose escalation of

infliximab is efficacious in patients with a low anti-infliximab antibody titer, while this approach may not be as effective for patients with a high titer because the anti-drug antibody cannot be overcome by the increased drug dose [19, 20]. For GLM, a recent study re-examined immunogenicity using banked blood samples



from previous phase 3 clinical trials with a highly sensitive assay, revealing that 24.9% of patients in the GO-FORWARD study were anti-GLM antibody positive, which was far higher than detected by the original assay [15]. However, this study also showed that the anti-GLM

antibody titers were predominantly low (< 1:100) and appeared to have no significant impact on the serum GLM concentration or the clinical response [15]. Therefore, it is hypothesized that dose escalation could be beneficial in most patients with an insufficient response to

◀**Fig. 4** Disease activity measures at 24 weeks stratified by the timing of GLM dose escalation. **a** Percentage of patients achieving a EULAR response at 24 weeks stratified by GLM dose escalation at the time point indicated. The clinical response to golimumab at 24 weeks was evaluated using the EULAR response criteria based on DAS28-CRP. A good or moderate response was defined as improvement of DAS28-CRP by > 1.2 from any baseline score or improvement by 0.6 – 1.2 from a baseline score of ≤ 5.1 . **b** Percentage of patients achieving remission as defined by the DA28-CRP (score < 2.6), SDAI (score ≤ 3.3), or CDAI (score ≤ 2.8). **c** Percentage of patients achieving low disease activity as defined by the DA28-CRP (score ≤ 3.2), SDAI (score ≤ 11), or CDAI (score ≤ 10). *EULAR* European League Against Rheumatism, *DAS28-CRP* Disease Activity Score 28 based on C-reactive protein, *CDAI* Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *REM* remission, *LDA* low disease activity, *GLM* golimumab

GLM at 50 mg, while a small group of patients with high anti-GLM antibody titers could possibly receive more benefit from switching to a different biologic agent. However, further studies are required to verify this hypothesis and to determine the predictors of clinically relevant reduction of the serum GLM concentration.

The present study revealed that 21.9% of patients discontinued GLM treatment even after dose escalation due primarily to the progression of disease, suggesting that dose escalation of GLM is not always effective. Therefore, it is crucial to identify characteristics of patients who would respond to GLM dose escalation after inadequate response to 50 mg of GLM. To this end, univariate and multivariate logistic regression analyses were employed. Our results suggested that dose escalation might be less effective in patients who have previously used biologics (OR 0.50, $p = 0.013$). It is widely believed that sequential switching to an alternative TNF inhibitor is effective for reducing disease activity, but the response is lower than with the first TNF inhibitor [21–25], probably because of channeling bias favoring patients with more severe disease [26]. Biologic-naïve patients are presumed to have lower disease activity than biologic-experienced patients,

thereby being more responsive to GLM dose escalation. In addition, our analysis also suggested that male sex predicted a clinical response to dose escalation (OR 2.37, $p = 0.015$). The reason why male sex was a positive predictor of a clinical response is not clear. However, it is interesting that several studies have identified male sex as a positive predictor of the clinical response to MTX [27–29]. Because approximately 80% of our study population was on concomitant MTX therapy, it is possible that concomitant use of MTX might have contributed to a better clinical response to dose escalation of GLM. On the other hand, concomitant use of MTX was not identified as an independent predictive factor by the present analysis, so further investigation of a larger sample size will be required to clarify the association between male sex and the clinical response to dose escalation.

The present analysis had some limitations as a retrospective study. First, the lack of blinding and randomization may have caused selection bias as well as response bias. In particular, decisions about dose escalation were made at the physician's discretion, potentially acting as a confounder. Second, the short study duration precluded us from conducting more thorough analyses of effectiveness and persistence. Third, we were unable to obtain data on patient characteristics at the time of dose escalation because of the design of the original PMS study, so we had to use the baseline patient characteristics. Thus, clinical improvement was evaluated by comparing disease activity at 24 weeks with that at baseline instead of activity at the time of dose escalation, preventing us from evaluating the improvement related to dose escalation per se. Furthermore, predictive factors were likewise determined by using baseline patient characteristics, but it would be more informative for daily clinical practice if we could identify useful predictors at the time of dose escalation. Finally, the effectiveness population of the current study included patients on GLM 50 mg monotherapy, which is not approved in Japan. This might have led to underestimation of effectiveness because those patients could have undergone dose escalation to 100 mg monotherapy, which is approved in Japan, for

Table 2 Univariate and multivariate logistic regression analyses of patient variables associated with discontinuation of GLM

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Demographics				
Age, years	1.01 (0.99, 1.03)	0.188	1.02 (0.99, 1.04)	0.148
Male, <i>n</i> (%)	2.18 (1.20, 3.97)	0.011	2.37 (1.18, 4.74)	0.015
Disease duration, years	1.00 (0.97, 1.02)	0.740	1.00 (0.98, 1.03)	0.745
Disease characteristics				
DAS28-CRP	1.02 (0.81, 1.29)	0.842	0.89 (0.69, 1.16)	0.396
Comorbidities, <i>n</i> (%)	0.59 (0.34, 1.00)	0.050	0.63 (0.33, 1.20)	0.162
Liver dysfunction	0.45 (0.23, 0.91)	0.026	0.47 (0.22, 1.01)	0.052
Renal dysfunction	1.46 (0.59, 3.64)	0.414	1.96 (0.67, 5.71)	0.210
Concomitant medications				
MTX	1.17 (0.69, 1.98)	0.563	1.24 (0.57, 2.70)	0.596
Oral corticosteroid	0.99 (0.62, 1.58)	0.971	1.11 (0.61, 2.00)	0.735
MTX + oral corticosteroid	1.36 (0.62, 3.02)	0.445	1.13 (0.33, 3.82)	0.848
Previous treatment				
Biologic therapy	0.50 (0.31, 0.82)	0.005	0.50 (0.29, 0.86)	0.013

CI confidence interval, *DAS28-CRP* Disease Activity Score 28 based on C-reactive protein, *MTX* methotrexate, *GLM* golimumab

reasons other than an inadequate response such as cost, since Japanese national health insurance only covers approved indications [9].

CONCLUSIONS

We demonstrated that RA patients with moderate to high disease activity experienced clinical improvement after dose escalation of GLM to 100 mg in real-world clinical practice. Our findings provide a critical insight into the effect of GLM dose escalation, which will facilitate more effective use of GLM in daily practice in Japan. However, use of a higher dose of GLM incurs a higher cost, consequently imposing a greater economic burden on the healthcare system. Therefore, further studies are required to more precisely identify the characteristics of

patients who would respond to GLM dose escalation and evaluate the balance between the clinical benefit versus economic burden of GLM dose escalation.

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Compliance with Ethics Guidelines. This article is based on previously conducted PMS study and does not contain any new interventional studies with human participants or animal subjects performed by any of the authors. The PMS study protocol and ethical considerations were assessed by the internal review board members and approved by the Japanese PMDA. This PMS study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, Identifier: UMIN000015895), was conducted in accordance with the Japanese regulations (Ministry of Health, Labor and Welfare Ministerial Ordinance No. 171) on Good Post-marketing Study Practice (GPSP), and was carried

out by Janssen Pharmaceutical K.K. after a contract with each study center.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due confidentiality clauses signed with participating medical institutions.

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