Rheumatol Ther (2020) 7:811–824
https://doi.org/10.1007/s40744-020-00228-1

ORIGINAL RESEARCH

Dose Adjustment of Methotrexate Administered Concomitantly with Golimumab for Rheumatoid Arthritis in Japanese Real-World Clinical Settings

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Received: June 26, 2020 / Published online: August 25, 2020

ABSTRACT

Introduction: The combination of methotrexate (MTX) with biological disease-modifying antirheumatic drugs (bDMARDs) is a recommended treatment option for rheumatoid arthritis (RA) patients showing an inadequate response to MTX monotherapy. However, the adequate dose of MTX, especially in long-term treatment with bDMARDs/MTX combination therapy, remains under-addressed. Since RA patients require long-term treatment, we examined the effects of using golimumab (GLM) in the long run as well as its persistency and associated factors.

Methods: We used the Japan Medical Data Center Inc. (JMDC) administrative claims data of 489 patients receiving GLM therapy for calculating the persistency in patients with constant, reduced, or escalated MTX dosing. The factors associated with GLM persistency were assessed using Cox proportional hazard modeling, controlling for the dose adjustment of concomitant MTX, age, sex, RA disease period, and the initial dose of GLM or concomitant MTX during GLM/MTX combination therapy.

Results: During GLM/MTX combination therapy, up to 52% of patients were reported to experience dose adjustments of concomitant MTX treatment (i.e., dose reduction and escalation in 34% and 18% of patients, respectively). Persistency was similar in the MTX dose-reduction patients and the MTX dose-constant patients. In the Cox proportional hazard model, no significant differences were observed in association with GLM persistency, including with respect to MTX dose adjustment.

Conclusions: GLM prescription was continued in 80% or more (1 year) and 50% or more (3 years) of RA patients receiving reduced concomitant MTX dosing, suggesting that MTX

Digital Features To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12765611.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40744-020-00228-1) contains supplementary material, which is available to authorized users.

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dose adjustment (including MTX reduction) could be considered in GLM/MTX combination therapy.

Keywords: Golimumab; JMDC database; Methotrexate; Rheumatoid arthritis

Key Summary Points

Why carry out this study?

The combination of methotrexate (MTX) with biological disease-modifying antirheumatic drugs (bDMARDs), such as golimumab (GLM), is a recommended treatment option for rheumatoid arthritis (RA) patients showing an inadequate response to MTX monotherapy.

However, the adequate dose of MTX, especially in long-term treatment with bDMARDs/MTX combination therapy, remains under-addressed.

What was learned from the study?

Roughly half of the RA patients treated with GLM underwent adjustments of concomitant MTX dosing in clinical practice.

At least 80% of those patients maintained reduced MTX dosing, and the persistency of GLM prescriptions was similar between the MTX dose-reduced patients and MTX dose-constant patients.

An MTX dose adjustment may be considered after controlling RA with long-term GLM/MTX combination therapy.

INTRODUCTION

Rheumatoid arthritis (RA) has been identified as a chronic inflammatory autoimmune disease that causes progressive joint destruction accompanied by declining health-related quality of life and increasing mortality [1]. The overproduction of cytokines secreted from active macrophages, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), largely contributes to the chronic synovitis observed in the RA patients [1]. In Japan, about 1.24 million individuals or 1.0% of the Japanese population have been reported to be suffering from RA [2]. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), sulfasalazine, leflunomide, and hydroxychloroquine have been used previously for the treatment of RA [3]. However, the recently developed biological disease-modifying antirheumatic drugs (bDMARDs), which are classified mainly by their target molecules and include TNF-α inhibitors and IL-6, B cell, and T-cell costimulation inhibitors, were reported to achieve low disease activity or even remission against moderate-to-severe RA [3, 4].

Golimumab (GLM), a fully human monoclonal anti-TNF-α antibody, targets a unique TNF-α epitope [5]. It binds to both the soluble and membrane-bound forms of TNF-α with a high affinity, creating stable complexes that prevent interactions between TNF-α and its receptors [6, 7]. GLM has been indicated for the treatment of patients with active RA [8], psoriatic arthritis [9], ankylosing spondylitis [10], ulcerative colitis [11], and nonradiographic axial spondyloarthritis [12] in many countries. In Japan, two GLM doses (50 mg or 100 mg), both of which are administered subcutaneously once every 4 weeks, have been approved for RA treatment since 2011.

The combination of MTX, the anchor drug for RA treatment, with bDMARDs is a recommended treatment option for RA patients showing an inadequate response to MTX monotherapy [3, 13, 14]. However, the optimal dose of MTX, especially during long-term treatment with bDMARDs/MTX combination therapy, remains an under-addressed subject. On the other hand, MTX is known to cause adverse events in a dose-dependent or dose-independent manner [15, 16]. Therefore, careful monitoring is a must during treatment with MTX. In Japan, a postmarketing surveillance (PMS) study on GLM (GLM-PMS study) for 6 months noted concomitant MTX use was present in about 80% of subjects among 5154

Japanese RA patients receiving GLM [17], and RA disease activity was significantly lowered in those patients with MTX dose reductions relative to those with MTX dose escalations. The study suggested further that the MTX dose was reduced or escalated during GLM/MTX combination therapy according to each patient's RA disease activity [18]. Although both efficacy and safety are considered to be reasons for MTX dose adjustment, it is of significant interest whether MTX dose adjustment could affect the persistency of GLM/MTX combination therapy.

Since the above GLM-PMS study results came from only 6 months of investigation, however, a long-term investigation of GLM/MTX combination therapy lasting beyond 6 months is needed to evaluate the impact of MTX dose adjustment on RA treatment outcomes.

METHODS

Data Source

We utilized commercially available administrative claims data from the Japan Medical Data Center Inc. (JMDC) databases, which contained approximately 560 million patients' data as of June 2018. The database consists of medical checkup and receipts data provided by multiple health insurance societies, which would support the tracking of hospital transfers and/or medications prescribed by different hospitals. The data used for this study were obtained from both acute- and chronic-phase hospitals throughout Japan. As JMDC database, the administrative claims data were available from January 2005. Therefore, we set the analysis period of the RA disease period (Table 1) and MTX prescription period (Tables 2, 3, and 4, Fig. 2a, b) as January 2005 to March 2018. On the other hand, the analysis period of GLM/MTX persistency was set as September 2011 to March 2018 given that GLM was approved in Japan in September 2011.

We utilized commercially available administrative claims data from the Japan Medical Data Center Inc. (JMDC) databases, which consists of medical checkup and receipts data provided by multiple health insurance societies. Informed patient consent was deemed unnecessary to obtain for this study because the data were de-identified by health insurance societies. Ethics approval was not required for our study.

Study Population and Study Design

The RA patients of the study population were identified according to the International Classification of Diseases, 10th revision, using the diagnosis codes M05, M06, and M080. Children younger than 18 years old and patients with diagnostic codes for diseases where TNF-α inhibitors are indicated as treatment—namely, Crohn's disease, psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile arthritis, ulcerative colitis, and/or Behçet's disease—were excluded. GLM was identified by the following National Health Insurance's drug list codes for MTX identification: 3999433G1024, 3,999,016, or 422,200. Eligible patients were required to receive at least 180 days of MTX prescription in combination with a fixed-dose prescription of GLM (50 or 100 mg) as this has been reported in BeSt [19], RRR [20], HONOR [21], and other studies that patients should maintain good disease control, such as low disease activity and remission, for at least 6 months after the start of treatment until initiating a dose reduction of the involved therapeutic drugs. The Japanese MTX guideline states that the MTX dose might be increased by 2 mg [22]. Therefore, in this study, we defined the dose adjustment as the MTX dose reduction or escalation of 2 mg. An MTX prescription interval of 120 days or more that occurred after GLM/MTX combination therapy initiation was defined as an MTX withdrawal period, and it was included in the GLM/MTX treatment period (Supplementary Fig. 1). Meanwhile, MTX discontinuation was defined as when GLM medication was continued for at least 120 days after the final MTX prescription (Supplementary Fig. 1). Patients treated with a fixed MTX dose during the concomitant prescription period were defined as MTX dose-constant patients, while those who received either a dose reduction or escalation at the first dose adjustment after GLM/MTX treatment initiation were defined as MTX dose-

Table 1 Characteristics of MTX dose-constant, dose-reduction, and dose-escalation patients receiving GLM

Characteristics	Overall (n = 174)	MTX dose-constant group (n = 83)	MTX dose-reduction group (n = 59)	MTX dose-escalation group (n = 32)
Age (years)	51.8 ± 11.0	52.3 ± 11.5	50.3 ± 10.3	53.2 ± 10.3
			(P = 0.281)	(P = 0.709)
Male/female sex (%)	32/142 (18%/82%)	18/65 (22%/78%)	8/51 (14%/86%)	6/26 (19%/81%)
			(p = 0.273)	(P = 0.803)
RA disease period (years)	4.4 ± 4.2	4.9 ± 4.3	4.3 ± 3.9	3.2 ± 4.0
			(P = 0.398)	(P = 0.061)
Drug history (%)				
bDMARDs	36 (32%)	26 (48%)	6 (17%)	4 (18%)
	(n = 112)	(n = 54)	(n = 36, P = 0.003)	(n = 22, P = 0.020)
MTX	109 (97%)	53 (98%)	35 (97%)	21 (95%)
	(n = 112)	(n = 54)	(n = 36, P = 1.000)	(n = 22, P = 0.498)
Glucocorticoid	61 (54%)	30 (56%)	21 (58%)	10 (45%)
	(n = 112)	(n = 54)	(n = 36, P = 0.831)	(n = 22, P = 0.458)
csDMARDs (except MTX)	25 (22%)	14 (26%)	6 (17%)	5 (23%)
	(n = 112)	(n = 54)	(n = 36, P = 0.438)	(n = 22, P = 1.000)

Patient characteristics at the initiation of GLM prescription. To compare the difference in characteristics between MTX dose-constant patients and MTX dose-reduction or dose-escalation patients, the Student's t test was performed for continuous variables and Fisher's exact test was applied for categorical variables. Drug history was analyzed in patients with data available from observation periods of at least 120 days before starting GLM prescription. The number of the study population is provided

csDMARDs conventional synthetic disease-modifying antirheumatic drugs, *bDMARDs* biological disease-modifying antirheumatic drugs, *GLM* golimumab, *MTX* methotrexate, *RA* rheumatoid arthritis

reduction or dose-escalation patients, respectively (Supplementary Fig. 2). MTX discontinuation and withdrawal were considered to be examples of MTX reduction (Supplementary Fig. 2). In the MTX dose-reduction group, patients receiving their first reduced MTX dose at least 180 days after the initiation of the GLM/MTX combination therapy were included in our analysis (Supplementary Fig. 3). Specifically, the following groups were included: (1) patients who underwent single (Supplementary Fig. 3a) or multiple MTX reductions without any escalations (Supplementary Fig. 3b) of which the final MTX reduction occurs at least 180 days after the initiation of combination therapy and (2) patients with MTX withdrawal or discontinuation occurring at least 180 days after the initiation of combination therapy (Supplementary Fig. 3c). Among MTX dose-reduction patients, those who maintained a lower MTX dose than the initial dose were identified as sustained MTX dose-reduction patients, whereas those who required an MTX dose prescription of greater than or equal to the initial dose were defined as unsustained MTX dose-reduction patients (Supplementary Fig. 4). The RA disease period was defined as the period from the initial diagnosis date to the first GLM

Table 2 Prescription of GLM and MTX in MTX dose constant, reduction, and escalation patients receiving GLM

Prescription	Overall (n = 174)	MTX dose-constant group (n = 83)	MTX dose-reduction group (n = 59)	MTX dose-escalation group (n = 32)
MTX prescription period (days)	1356 ± 693	1244 ± 638	1540 ± 697	1306 ± 751
			(P = 0.010)	(P = 0.662)
Initial MTX dose during GLM/MTX combination therapy (mg)	8.6 ± 3.4	8.4 ± 3.4	9.9 ± 2.9	6.7 ± 3.1
			(P = 0.009)	(P = 0.016)
Final MTX dose during GLM/MTX combination therapy (mg)	7.8 ± 3.1	8.4 ± 3.4	6.5 ± 2.3	8.5 ± 3.1
			(P < 0.001)	(P = 0.896)
Period from initial date of GLM/MTX combination therapy to dose-adjustment date of MTX (days)	NA	NA	418 ± 309	266 ± 318
MTX-withdrawal patients (%)	6 (3%)	0 (0%)	6 (10%)	0 (0%)
			(P = 0.004)	(P = 1.000)
MTX-discontinuation patients (%)	4 (2%)	0 (0%)	4 (7%)	0 (0%)
			(P = 0.028)	(P = 1.000)
Patients treated with 50 mg of GLM (%)	150 (86%)	72 (87%)	50 (85%)	28 (88%)
			(P = 0.809)	(P = 1.000)
GLM prescription period (days)	761 ± 507	525 ± 348	1033 ± 519	868 ± 546

To compare the difference in MTX and GLM prescription between MTX dose-constant and MTX dose-reduction or dose-escalation patients, the Student's t test was performed for continuous variables and Fisher's exact test was applied for categorical variables. The significance for the GLM prescription period was not calculated because it was evaluated with the log-rank test as shown in Fig. 2

GLM golimumab, *RA* rheumatoid arthritis, *MTX* methotrexate, *NA* not analyzed

prescription date. Missing data were not included and compensated for. The prescription data indicating the administration of 0 mg of GLM were removed from this analysis. Estimation and exclusion of outlier values were not conducted.

Drug treatment history prior to the initial GLM prescription was evaluated for the period from 120 days before GLM prescription initiation to a day before the start date. The involved bDMARDs, other than GLM, included abatacept (World Health Organization Anatomical Therapeutic Chemical [WHO ATC] code: L04AA24), etanercept (WHO ATC code: L04AB01), infliximab (WHO ATC code: L04AB02), adalimumab (WHO ATC code: L04AB04), certolizumab pegol (WHO ATC code: L04AB05), tocilizumab (WHO ATC code: L04AC07), and sarilumab (WHO ATC code: L04AC14). Glucocorticoids (GCs) were identified by the WHO ATC code H02AB. csDMARDs except for MTX were identified as those drugs with the WHO ATC code M01C.

Definition of Persistency

Persistency was defined as the time that elapsed from treatment initiation until the discontinuation of GLM. We defined the treatment initiation date as the date of the first GLM prescription in the database. We used a

Table 3 Univariate Cox proportional hazard model for MTX dose-constant and dose-reduction patients receiving GLM

Patient characteristics	Hazard ratio (95% confidence interval)	*P* value
MTX dose reduction (vs. MTX dose constant)	0.89 (0.50–1.60)	0.701
Male sex (vs. female)	1.34 (0.74–2.42)	0.341
Age $\geq$ 60 years (vs. $<$ 60 years)	0.85 (0.46–1.57)	0.602
RA disease period, years (initial diagnosis date to GLM start date)	0.97 (0.91–1.03)	0.293
Initial dose of GLM 50 mg (vs. 100 mg)	0.77 (0.41–1.44)	0.413
Initial MTX dose during GLM/MTX combination therapy $>$ 8 mg (vs. $\leq$ 8 mg)	1.14 (0.70–1.87)	0.593

GLM golimumab, *MTX* methotrexate, *RA* rheumatoid arthritis

Table 4 Univariate Cox proportional hazard model for MTX dose-constant and dose-escalation patients receiving GLM

Patient characteristics	Hazard ratio (95% confidence interval)	*P* value
MTX dose escalation (vs. MTX dose constant)	0.90 (0.49–1.66)	0.732
Male sex (vs. female)	0.82 (0.42–1.58)	0.550
Age $\geq$ 60 years (vs. $<$ 60 years)	0.85 (0.48–1.52)	0.588
RA disease period, years (initial diagnosis date to GLM start date)	1.00 (0.94–1.07)	0.973
Initial dose of GLM 50 mg (vs. 100 mg)	0.70 (0.34–1.44)	0.333
Initial MTX dose during GLM/MTX combination therapy $>$ 8 mg (vs. $\leq$ 8 mg)	1.58 (0.92–2.72)	0.095

GLM golimumab, *MTX* methotrexate, *RA* rheumatoid arthritis

prescription interval of 60 or more days to define prescription discontinuation. This definition of persistency is consistent with other claims data studies on RA [23–25]. With the limited number of patients in this study, we included censored cases, which were defined as patients who received a GLM prescription from 60 days before the observation end date up to the observation end date.

Statistical Analysis

To evaluate differences between patient groups, the Student's *t* test was performed to compare continuous variables and Fisher's exact test for categorical variables. Unless otherwise stated, results are presented as means ± standard deviations. The following survival analyses were conducted with MTX dose adjustment established as a time-dependent covariate. The Simon and Makuch method was adopted to estimate the survival function for the GLM persistency.

Differences in persistency were tested for significance using the Mantel–Byar test. A *P* value of less than 0.05 was considered to be statistically significant. To analyze the factors associated with persistency, a univariate Cox proportional hazard model was employed, which included sex, age, RA period, the initial GLM dose, and the initial MTX dose after

starting the combination prescription with GLM. Then, a multivariate Cox proportional hazard model including MTX dose adjustment and factors with *P* values of less than 0.20 in the univariate analysis was established. The factors associated with persistency in the MTX dose-reduction and dose-constant groups were examined by considering the combined population of these groups, while factors associated with persistency in the MTX dose-escalation and dose-constant groups were assessed using the combined population of these two groups. No adjustment for multiplicity was made because all analyses were conducted in an exploratory manner. The analyses were performed using the RStudio software (version 1.1.463) [26] and EZR (Saitama Medical Centre, Jichi Medical University; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html; Kanda, 2012) [27].

RESULTS

Study Population

By applying the inclusion criteria and definitions described in "Methods", we were able to identify 83 MTX dose-constant, 59 MTX dose-reduction, and 32 MTX dose-escalation patients (Fig. 1), indicating that 52% of the total patient population had experienced an MTX dose adjustment of some kind during GLM/MTX combination therapy. The MTX dose-reduction patients (34% of the total patient population) were further subclassified into 50 sustained MTX dose-reduction patients (approximately 80% of the MTX dose-reduction patients) and 9 unsustained MTX dose-reduction patients (Fig. 1).

Patient Characteristics

The patient characteristics of the entire study population, including MTX dose-constant, dose-reduction, and dose-escalation patients, are provided in Table 1. The MTX dose-reduction/dose-escalation patient characteristics were compared with those of the MTX dose-constant patients. Our findings show that age and sex did not significantly vary between the groups. Among all the patients, the average age of the patient population was slightly above 50 years, and approximately 80% of the patients were female. We also investigated patients' drug and disease histories. The study population was restricted to patients with data from observation periods of at least 120 days before the first GLM prescription. Treatment with bDMARDs before starting GLM was conducted in 32% of patients. Ultimately, the prevalence of patients receiving bDMARDs prior to GLM was found to be significantly lower in the MTX dose-reduction (17%) and dose-escalation (18%) groups than in the MTX dose-constant group (48%). Prior to GLM treatment, 95% or more of the patients were treated with MTX, and half of the patients were pretreated with GCs. Approximately 20% of the patients had been given prescriptions for csDMARDs, not including MTX, prior to GLM initiation.

We next scrutinized MTX prescriptions in the study population, with details presented in Table 2. Overall, the MTX prescription period was found longer among MTX dose-reduction patients (1540 days) compared with MTX dose-constant patients (1244 days). Further, the initial MTX dose during GLM/MTX combination therapy was higher in the MTX dose-reduction group (9.9 mg) than in the MTX dose-constant group (8.4 mg), whereas the final MTX dose during combination therapy was lowest in the MTX dose-reduction group (6.5 mg). MTX dose-escalation patients (6.7 mg) received an initial MTX dose that was lower than that administered to MTX dose-constant patients, while the final MTX dose was found to be similar between these groups. The timing of the initial dose adjustment was later among MTX dose-reduction patients (418 days) than MTX dose-escalation patients (266 days). Among the 59 MTX dose-reduction patients, six patients (10%) experienced MTX withdrawal, and four patients (7%) discontinued MTX.

Persistency of GLM Prescription

As shown in Table 2, most patients ($\geq$ 85%) received 50 mg of fixed-dose GLM regardless of

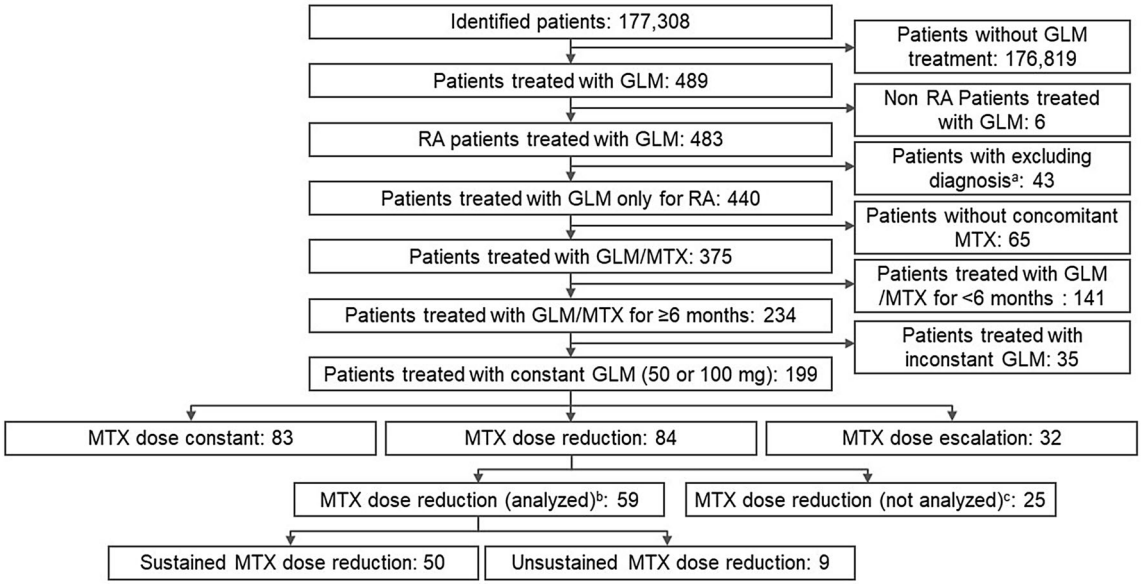

Fig. 1 Study population. [a]Children younger than 18 years and patients with Crohn's disease, psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile arthritis, ulcerative colitis, and/or Behçet's disease were excluded. [b]Patients receiving reduced MTX at least 180 days after the initiation of GLM/MTX combination therapy were included in the analysis. The following patients were included: (1) patients undergoing multiple MTX reductions without any escalations for at least 180 days between the initiation of combination therapy and the final MTX reduction and (2) patients with MTX withdrawal or discontinuation occurring at least 180 days after the initiation of combination therapy. [c]Twenty-five patients out of 84 MTX dose reduction were excluded, because these patients experienced MTX dose reduction, dose escalation and then dose reduction again. *GLM* golimumab, *MTX* methotrexate, *RA* rheumatoid arthritis

whether or not they experienced a dose adjustment. MTX dose-reduction (1033 days) and dose-escalation (868 days) patients had longer GLM prescription periods when compared with MTX dose-constant patients (525 days). We then analyzed persistency using the Simon–-Makuch estimator of survival function; Simon–Makuch curves of GLM prescription-retention comparing MTX dose-constant and dose-reduction patients and MTX dose-constant and dose-escalation patients are presented in Figs. 2a and b, respectively. The persistency was more similar among MTX dose-reduction and dose-escalation patients relative to that among MTX dose-constant patients. One-year persistency was 82.9% (95% confidence interval [CI] 76.3–90.1%) for MTX dose-constant patients versus 85.2% (95% CI 71.1–100%) for MTX dose-reduction patients (Fig. 2a) and 77.9% (95% CI 69.8–87.0%) for MTX dose-constant patients versus 76.3% (95% CI 60.2–96.7%) for MTX dose-escalation patients (Fig. 2b).

To further assess the differences in persistency, as mentioned before, we employed a univariate Cox proportional hazard model. No significant differences (*P* value was greater than 0.20) were observed in association with GLM discontinuation, sex, age, RA disease period, the initial GLM prescription dose, and the initial MTX dose during GLM/MTX combination therapy for MTX dose-constant and dose-reduction patients receiving GLM (Table 3). For MTX dose-constant and dose-escalation patients receiving GLM, *P* value of initial MTX dose during GLM/MTX combination therapy was less than 0.20 (Table 4). The multivariate Cox proportional hazard models with MTX dose adjustment (MTX dose-constant or dose-escalation) and initial MTX dose during GLM/MTX combination therapy was performed. For

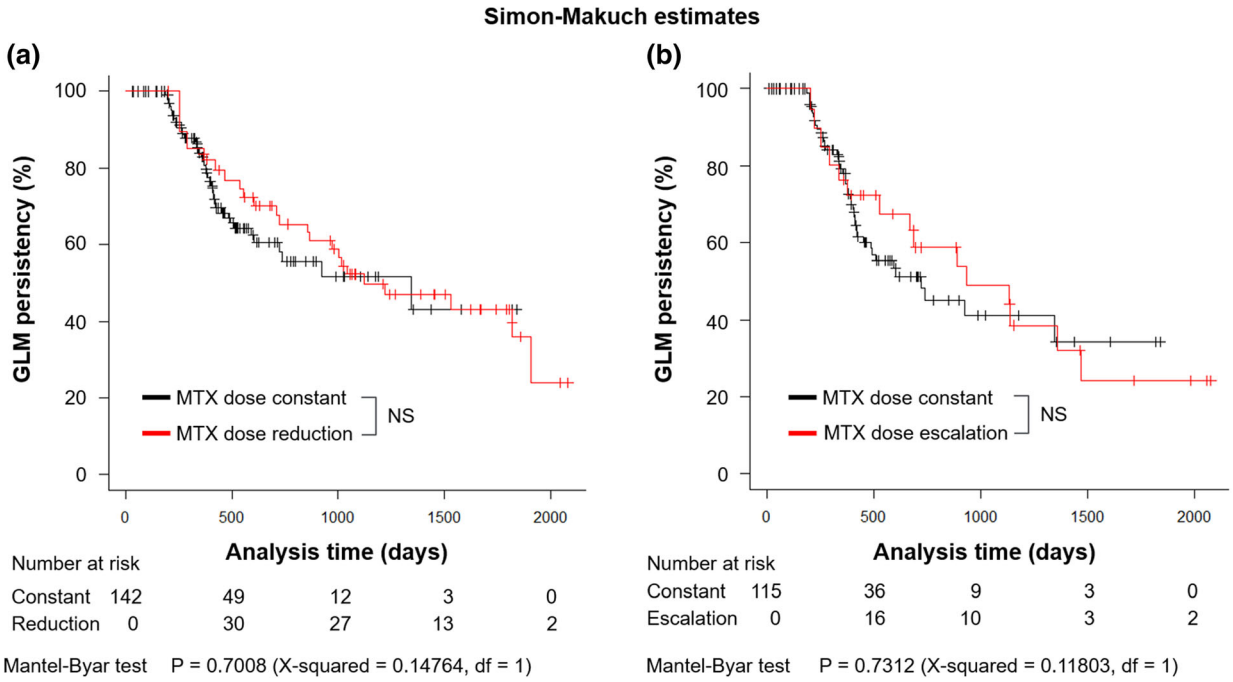

Fig. 2 **a** Simon–Makuch curves for MTX dose-constant and MTX dose-reduction patients receiving GLM. **b** Simon–Makuch curves for MTX dose-constant and MTX dose-escalation patients receiving GLM. To compare the difference in GLM persistency between MTX dose-constant patients and MTX dose-reduction or dose-escalation patients, the Mantel–Byar test was performed without consideration for multiplicity. *GLM* golimumab, *MTX* methotrexate, *NS* not significant

both factors, the statistically significant differences in persistency were not observed (Table 5).

DISCUSSION

Dose Adjustment of Concomitant MTX in Patients Receiving GLM

In a clinical trial of GLM for RA in Japan, GLM/MTX combination therapy prompted significant improvements in clinical manifestations regardless of the GLM dose (50 mg or 100 mg) or concomitant MTX use (with or without) [28, 29]. However, although most patients may respond to GLM/MTX combination therapy, the individual MTX dose that is ideal for each patient still remains unclear, with implications especially in daily clinical practice. In the aforementioned clinical trial, which compared the benefit of high-dose MTX (20 mg/week) and low-dose MTX (7.5 mg/week) in adalimumab/MTX combination therapy, the high-dose MTX group failed to show inferiority in disease activity control and superiority in patient-reported outcomes [30]. As such, a dose adjustment of MTX after the initiation of bDMARDs/MTX combination therapy might be applicable in clinical practice.

In the GLM-PMS study, RA disease activities among patients with MTX dose adjustments completed before and at the end of the GLM treatment period were evaluated [18]. In this study, patients with MTX dose reductions did not exhibit worsened RA disease activity relative to MTX dose-constant patients, while MTX dose-escalation patients tended to be inferior to MTX dose-constant patients in this regard [18]. However, because the GLM-PMS study was limited to a period of 6 months [18], the efficacy of the concomitant MTX dose adjustment with respect to long-term treatment outcomes in RA remained unexplored. In the present study, we

Table 5 Multivariate Cox proportional hazard model for MTX dose-constant and dose-escalation patients receiving GLM

Patient characteristics	Hazard ratio (95% confidence interval)	*P* value
MTX dose escalation (vs. MTX dose constant)	0.91 (0.49–1.68)	0.766
Initial MTX dose during GLM/MTX combination therapy > 8 mg (vs. ≤ 8 mg)	1.58 (0.92–2.71)	0.098

GLM golimumab, *MTX* methotrexate

queried the JMDC administrative claims database to obtain details on GLM persistency for evaluating the long-term RA treatment outcome in patients with concomitant MTX dose adjustments. Our findings support the earlier GLM-PMS study results by demonstrating that RA treatment outcomes were not worsened in MTX dose-reduction patients as compared with among subjects receiving a constant MTX dose [18]. Our results also support the GLM-PMS study results by indicating a similar persistency profile existed among MTX dose-escalation patients and MTX dose-constant patients. Overall, these results suggest that RA treatment was optimized by adjusting the concomitant MTX dose, while Cox regression analysis did not find any factors that worsened the GLM persistency, including MTX dose adjustment (i.e., dose reduction or increase). Hence, our study provides critical new insight into the relationship between concomitant MTX dose and long-term use of GLM/MTX combination therapy, which was not addressed in the previous GLM-PMS study [18].

Baseline Predictors for Dose Adjustment of Concomitant MTX

In this study, Cox proportional hazard modeling did not identify factors associated with maintaining the GLM prescription. To further determine baseline predictors for MTX dose adjustment, a potential association with patients' drug and disease history was examined using logistic regression analysis. The study population was then restricted to include patients with data available from observation periods of at least 120 days before the first GLM prescription. In the multivariate model, both a higher initial dose of MTX during GLM/MTX combination therapy ($P < 0.01$) and no history of bDMARDs treatment ($P < 0.05$) were associated with MTX dose reduction (data not shown). Consistently, the presence of no bDMARDs history was also correlated with MTX dose reduction in the GLM-PMS study [18]. In addition, a higher GLM persistency in biologic-naïve patients as compared with that in patients who continued to receive bDMARDs [23] suggested that biologic-naïve patients tended to have a good prognosis and reduced concomitant MTX dosing. Renal impairment was associated with MTX dose reduction in the GLM-PMS study [18]. However, we could not evaluate subjects with renal impairment in this study because clinical data of serum creatinine levels were rarely obtained from the JMDC database. Further studies with larger numbers of patients are required. Furthermore, 8 mg or less of the initial dose of concomitant MTX ($P < 0.05$) and no bDMARD history ($P < 0.05$) were related to MTX dose escalation (data not shown). However, in the Cox proportional hazard model, the rate of GLM persistency tended to be higher in patients treated with 8 mg or less of MTX at the time of initial prescription during GLM/MTX combination therapy, albeit without statistical significance. These results support that patients with GLM/MTX combination therapy are more likely to require escalation of a lower initial dose of MTX.

Limitations

Several limitations of this study should be considered. First, clinical indices for RA disease

activity, such as the Disease Activity Score in 28 joints (DAS28), and laboratory evidence indicating the serum levels of C-reactive protein and erythrocyte sedimentation rate were not included in the JMDC database. Therefore, persistency was used for evaluating the treatment outcome. Although we showed a lower 1-year persistency outcome of GLM (approximately 50%) by including the 6-month follow-up period after the initiation of GLM prescription to remove patients with unstable disease activity, a better GLM persistency (91.2%) was reported in the actual usage investigation of bDMARDs in Japan that adopted at minimum 12 months for the follow-up period [23]. In addition, because RA disease activity dominantly seems to affect the decision about MTX dose adjustment, a lack of details about this parameter among the patient characteristics is detrimental. Second, we could not determine the reasons for discontinuation of GLM treatment—for example, it could be due to adverse events, a lack of efficacy, clinical remission, or another reason (e.g., economic burden). Similarly, we also could not determine the reason for the dose adjustment of concomitant MTX, which may include disease control, exacerbation of RA, occurrence of adverse events, or problems with treatment adherence. In addition, dose adjustments for anti-rheumatic drugs (e.g., glucocorticoids or other antirheumatic drugs) other than GLM/MTX have not been analyzed in this study. Third, the JMDC database consists of receipts data provided by health insurance societies, while data for patients 75 years of age or older, who form a large portion of Japanese RA patients, are not included in this database. The age average was relatively lower in this study (around 50 years) than that in the GLM-PMS study and in a separate analysis that addressed the persistency of bDMARDs, including GLM, using a hospital claims database different than the JMDC (approximately 60 years) [18, 23]. Therefore, our results are not necessarily representative of the daily practice of RA treatment in Japan. Fourth, the dose of concomitant MTX therapy in Japan is reportedly lower than that in other countries. While an MTX dose increase of 20–30 mg/week is recommended overseas, the upper-limit MTX dose was 8 mg/week until 2011 in Japan [31, 32]. The use of MTX doses higher than 8 mg/week was approved in 2011 in Japan, and the MTX clinical practice guideline in Japan indicates that the target increase dose of MTX is 10–12 mg/week [22]. Therefore, Japanese physicians can consider pursuing the concomitant use of GLM after an MTX dose exceeding 8 mg is administered. In fact, the mean concomitant MTX dose at the initiation of GLM prescription in this study was 8.6 mg/week.

CONCLUSIONS

Based on a long-term investigation using administrative claims data in Japan, we were able to determine that roughly half of the patients treated with GLM had undergone adjustments of concomitant MTX dosing in clinical practice. Furthermore, the analysis demonstrated that at least 80% of those patients maintained reduced MTX dosing, and the persistency of GLM prescriptions was not diminished among the MTX dose-reduction patients when compared with among MTX dose-constant patients, suggesting that an MTX dose adjustment could be considered after controlling RA with long-term GLM/MTX combination therapy. However, in this study, we did not identify baseline factors associated with the persistency of GLM prescriptions.

ACKNOWLEDGEMENTS

The authors would like to thank Yutaka Ishii and Seiji Yokoyama (Immunology, Infectious Diseases and Vaccine Department, Medical Affairs Division, Janssen Pharmaceutical K.K.) for their contribution to the study design and data interpretation. The authors also thank Akinori Takahashi, Tatsuro Sudo, Taichi Kido, and Seiji Kawa from Deloitte Tohmatsu Consulting LLC for their support in conducting statistical analysis and assistance with medical writing. We also thank International Medical Translation Service, Inc. for English-language editing.

Funding. Sponsorship for this study and the Rapid Service Fees were jointly provided by Mitsubishi Tanabe Pharma Corporation (Osaka, Japan) and Janssen Pharmaceutical K.K. (Tokyo, Japan).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Fumiko Yamairi, Toshiro Yano, Takashi Goto and Tomohisa Iwasakiare employed at Mitsubishi Tanabe Pharma Corporation.

Compliance with Ethics Guidelines. We utilized commercially available administrative claims data from the Japan Medical Data Center Inc. (JMDC) databases, which consists of medical checkup and receipts data provided by multiple health insurance societies. Informed patient consent was deemed unnecessary to obtain for this study because the data were de-identified by health insurance societies. Ethics approval was not required for our study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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