

[ORIGINAL ARTICLE]

Effectiveness and Safety of Golimumab for Patients ≥ 75 Years Old with Rheumatoid Arthritis

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Abstract:

Objective Treatment of elderly patients with rheumatoid arthritis (RA) has been controversial because they often have serious comorbidities and cannot use methotrexate (MTX). In Japan, golimumab (GLM) 100 mg without MTX is approved. We investigated the effectiveness and safety of GLM in elderly patients with RA.

Methods The GLM survival rate was evaluated using the Kaplan-Meier method. Disease activities, laboratory findings, and treatments were evaluated.

Patients We enrolled 168 patients with RA in our hospital. Using age ≥ 75 years old to identify elderly patients, younger (n=111) and elderly (n=57) groups were established. Elderly patients were divided into 2 groups according to the MTX treatment status (with, n=27; without, n=25).

Results The GLM survival rates were 80.8% and 82.3% in elderly and younger patients, respectively (p=0.762). At 52 weeks, the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) was improved in elderly patients (4.26 vs. 3.31, p<0.001); the Health Assessment Questionnaire Disability Index (HAQ-DI) was unchanged (1.12 vs. 0.88, p=0.694). When elderly patients were compared according to the MTX treatment status, the DAS28-ESR had improved in both groups (with MTX: 3.82 vs. 2.68, p<0.001; without MTX: 4.76 vs. 4.25, p=0.026); however, the HAQ-DI had not. The GLM survival rates at 52 weeks were 85% and 76% in patients with and without MTX, respectively.

Conclusion In elderly patients with RA, GLM was effective, regardless of MTX treatment status, but it did not affect the HAQ-DI. GLM survival rates were comparable between elderly and younger patients. GLM may be a suitable option for elderly patients with RA who cannot use MTX.

Key words: rheumatoid arthritis, golimumab, elderly patients, methotrexate

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Introduction

There is an increasing number of elderly patients with newly diagnosed rheumatoid arthritis (RA), and the mean age of patients with RA has also been increasing in recent years (1). Furthermore, young patients with RA are reaching older ages because of an improved prognosis among those patients (2, 3). Elderly patients with RA have more comorbidities than do young patients with RA (2). Renal failure is

a severe comorbidity among elderly patients with RA. The renal function of patients with RA worsens with age (4, 5) and must be carefully monitored during the treatment of elderly patients with RA.

A critical problem during the treatment of elderly patients with RA involves the usage of methotrexate (MTX), which is an anchor drug in RA treatment. According to the Japan College of Rheumatology guideline, the use of MTX is contraindicated for patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², and careful admini-

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stration is necessary for patients with an eGFR <60 mL/min/1.73 m² (6). According to the 2019 European League Against Rheumatism guideline (7), patients with phase I treatment failure are recommended to receive biological disease-modifying anti-rheumatic drugs or Janus kinase inhibitor in phase II treatment. For patients with RA who cannot receive MTX treatment (e.g. because of chronic kidney disease), interleukin-6 receptor (IL-6R) inhibitors are recommended (7). However, IL-6 inhibition interferes with the identification of infection [e.g., fever onset and C-reactive protein (CRP) elevation] (8). This can delay the awareness of infection, especially in elderly patients. Janus kinase inhibitors represent another treatment option; however, in the 2020 RA guideline published by the Japan College of Rheumatology, biological disease-modifying anti-rheumatic drugs were stated as preferred over Janus kinase inhibitors, because of their long-term safety (9).

Another limitation of treatment with IL-6R inhibitors (e.g. tocilizumab) is that patients receiving such treatment have a greater risk of lower gastrointestinal perforation than those not receiving them (10, 11). Patients with diverticulitis reportedly have an increased risk of lower intestinal perforation and should avoid the use of tocilizumab (12). Patients with failed IL-6R inhibitor treatment also require other biological disease-modifying anti-rheumatic drugs.

Golimumab (GLM; approved in 2011 in Japan) is another option for the treatment of patients with RA who cannot receive IL-6R therapy. GLM does not require combination with MTX, in contrast to other tumor necrosis factor- α inhibitors, such as infliximab and adalimumab. In Japan, the use of 100 mg GLM without MTX has been approved. Monotherapy with 100 mg GLM has demonstrated disease improvement comparable to the effects achieved with GLM 50 mg + MTX (13). In the GO-MONO study, GLM monotherapy resulted in good clinical and radiographic improvements (14). We previously reported the long-term use of GLM at Niigata Rheumatic Center (15); specifically, we described improvements in grip power associated with GLM treatment. In another study of real-world clinical data, Okazaki et al. reported that the safety and effectiveness of GLM treatment were nearly identical between elderly and younger patients (16). In their article, elderly patients with RA were defined as those ≥ 75 years old; the GLM survival rate among the elderly patients at 24 weeks after initiation of treatment was 74.7%, which was significantly lower than the GLM survival rate among younger patients (78.0%). However, even though the GLM survival rate was lower among elderly patients than among younger patients, GLM remains an important alternative when MTX and IL-6R inhibitor treatments cannot be used.

To our knowledge, there have been few studies regarding the use of GLM in elderly patients, especially those ≥ 75 years old; furthermore, little is known regarding GLM use in elderly patients without concomitant MTX treatment in real-world clinical practice. In this study, we evaluated the effectiveness and safety of GLM in elderly patients ≥ 75

years old over a treatment period of 52 weeks. In addition, we evaluated the effectiveness and safety of GLM according to the MTX treatment status.

Materials and Methods

This study enrolled 168 patients with RA who began treatment with GLM from November 2011 to August 2018 in Niigata Rheumatic Center. The data were retrospectively collected from medical records. All patients were diagnosed in accordance with the 2010 American College of Rheumatology/European League Against Rheumatism criteria (17). Patients were divided into younger and elderly groups, using age ≥ 75 years old to define the elderly group, in accordance with the definition of the Japan Gerontological Society and the Japan Geriatrics Society (18). This study was conducted in accordance with the Declaration of Helsinki. Consent was obtained by the optout method at Niigata Rheumatic Center. This study protocol was approved by the ethics committee in Niigata Rheumatic Center.

We collected data regarding disease activity [i.e., Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR), DAS28-CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index, tender joint count, swollen joint count, Health Assessment Questionnaire Disability Index (HAQ-DI), Evaluator's Global Assessment, Patient's Global Assessment, Steinbrocker class, and Steinbrocker stage (19)], body weight, disease duration, laboratory findings [i.e. creatinine, CRP, ESR, matrix metalloproteinase-3 (MMP-3), rheumatoid factor, anti-cyclic citrullinated peptide antibody], and treatment [i.e. GLM, prednisolone (PSL), and MTX dosage]. Creatinine clearance (Ccr) was calculated with the Cockcroft-Gault Equation. All data were collected at the onset of GLM treatment and after 52 weeks of GLM treatment.

The Mann-Whitney U test was used to compare patient characteristics between younger and elderly patients. Wilcoxon's signed-rank test was used to compare patient characteristics before and after GLM treatment. Fisher's exact test was used to evaluate differences in proportions between two groups. The GLM survival rate was evaluated with the Kaplan-Meier method. Two-sided p values <0.05 were considered statistically significant.

All statistical analyses were performed with the EZR software program (20). All values represent the median (interquartile ratio), unless otherwise specified.

Results

In total, 57 and 111 patients were classified into the elderly and younger groups, respectively (Table 1). The median ages were 79 and 65 years old in the elderly and younger groups, respectively. The HAQ-DI (p=0.018) and MMP-3 (p=0.002) values were significantly greater in elderly patients than in younger patients; however, the DAS28-ESR, DAS28-CRP, Clinical Disease Activity Index, and SDAI values did

Table 1. Baseline Characteristics of Patients Treated with GLM.

	Elderly patients (n=57)	Younger patients (n=111)	p value
Age (years old)	79 (76-81)	65 (59-70)	<0.001
Sex (female, %)	80.7	77.5	0.695
DAS28-ESR	4.35 (3.58-5.30)	4.19 (3.25-5.00)	0.237
DAS28-CRP	3.93 (3.22-4.68)	3.63 (2.88-4.31)	0.080
CDAI	14.0 (10.6-23.0)	13.8 (8.9-20.4)	0.288
SDAI	15.2 (11.5-25.1)	14.9 (9.5-23.0)	0.159
HAQ-DI	1.13(0.38-2.00)	0.75 (0.13-1.25)	0.018
TJC	3 (2-7)	2 (1-5)	0.230
SJC	3 (0-5)	2 (1-5)	0.597
EGA	35 (20-50)	40 (20-52)	0.670
PGA	46 (29-66)	47 (21-63)	0.309
Steinbrocker Stage I+II/III+IV (%)	33.3/ 66.7	34.2/ 65.8	1.000
Steinbrocker Class I+II/III+IV (%)	45.6/ 54.4	68.5/ 31.5	0.005
Body Weight (kg)	48.4 (41.7-53.0)	52.0 (45.7-61.9)	<0.001
Cr (mg/dL)	0.68 (0.55-0.84)	0.58 (0.51-0.74)	0.021
eGFR (mL/min/1.73m ²)	69.8 (49.5-84.0)	82.7 (66.5-96.6)	<0.001
Ccr (mL/min.)	53.7 (41.5-64.7)	87.1 (64.4-98.8)	<0.001
Disease duration (years)	11 (4-21)	10 (4-17)	0.371
bDMARDs naïve (%)	54.4	52.3	0.871
PSL usage (%)	75.4	71.2	0.589
PSL dosage (mg/day)	5.0 (3.0-5.8)	4.5 (3.0-5.0)	0.212
MTX usage (%)	47.4	72.1	0.002
MTX dosage(mg/week)	6 (6-8)	8 (8-10)	0.007
GLM dosage(100mg, %)	38.6	37.8	1.000
CRP (mg/dL)	1.1 (0.2-3.7)	0.7 (0.2-2.1)	0.115
ESR (mm/hr)	33 (14-76)	27 (14-52)	0.262
MMP-3 (ng/mL)	199.3 (112.3-300.5)	128.1 (74.6-215.9)	0.002
RF (IU/L)	37 (9-97)	46 (16-142.5)	0.282
Anti-CCP antibody (U/mL)	76.6 (10.0-188.6)	75.7 (19.4-168.8)	0.470

DAS28-ESR: Disease Activity Score 28-erythrocyte sedimentation rate, DAS28-CRP: Disease Activity Score 28-C-reactive protein, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, HAQ-DI: Health Assessment Questionnaire Disability Index, TJC: tender joint count, SJC: swollen joint count, EGA: Evaluator's Global Assessment, PGA: Patient's Global Assessment, Cr: creatinine, eGFR: estimated glomerular filtration rate, Ccr: creatinine clearance, bDMARDs: biological disease-modifying anti-rheumatic drugs, PSL: prednisolone, MTX: methotrexate, GLM: golimumab, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, RF: rheumatoid factor, CCP: cyclic citrullinated peptide

Values are shown as median (interquartile range) unless otherwise specified.

not significantly differ between groups. The eGFR ($p<0.001$) and Ccr ($p<0.001$) values were lower in elderly patients than in younger patients. The proportion of patients who received MTX was greater in the younger group than in the elderly group ($p=0.002$), as was the MTX dosage ($p=0.007$). There were no significant differences between groups in the proportions of patients treated with PSL, the PSL dosage, and proportions of patients treated with 100 mg GLM.

Fig. 1 shows the numbers of patients who discontinued GLM within 52 weeks, as well as their reasons for discontinuation. Five elderly patients and two younger patients were excluded from the evaluation of the survival rate because they transferred to another hospital or were missing data. Of the remaining 52 elderly patients, 10 (19.2%) discontinued GLM within 52 weeks because of ineffectiveness in 6 (11.5%) and comorbidities in 4 (7.7%). These comor-

bidities included infection (one patient with pneumonia and one patient with an infection of unknown origin), low back pain (one patient), and heart failure (one patient). Of the remaining 109 younger patients, 19 (17.4%) discontinued GLM within 52 weeks because of ineffectiveness (12 patients, 11.0%); rash (3 patients, 2.8%); multiple sclerosis, psoriasis, and malignancy (1 patient each, 0.9%); and high cost (1 patient, 0.9%). The GLM survival rates were 80.8% and 82.3% in elderly and younger patients, respectively.

Fig. 2 shows the Kaplan-Meier curves of the GLM survival rate over 52 weeks; the GLM survival rate did not significantly differ between groups ($p=0.762$).

Fig. 3 shows the disease activities, laboratory findings, PSL dosage, and MTX dosage at the onset of GLM administration and at 52 weeks after the initiation of treatment in elderly patients with RA. The DAS28-ESR [4.26 (3.56-5.15)

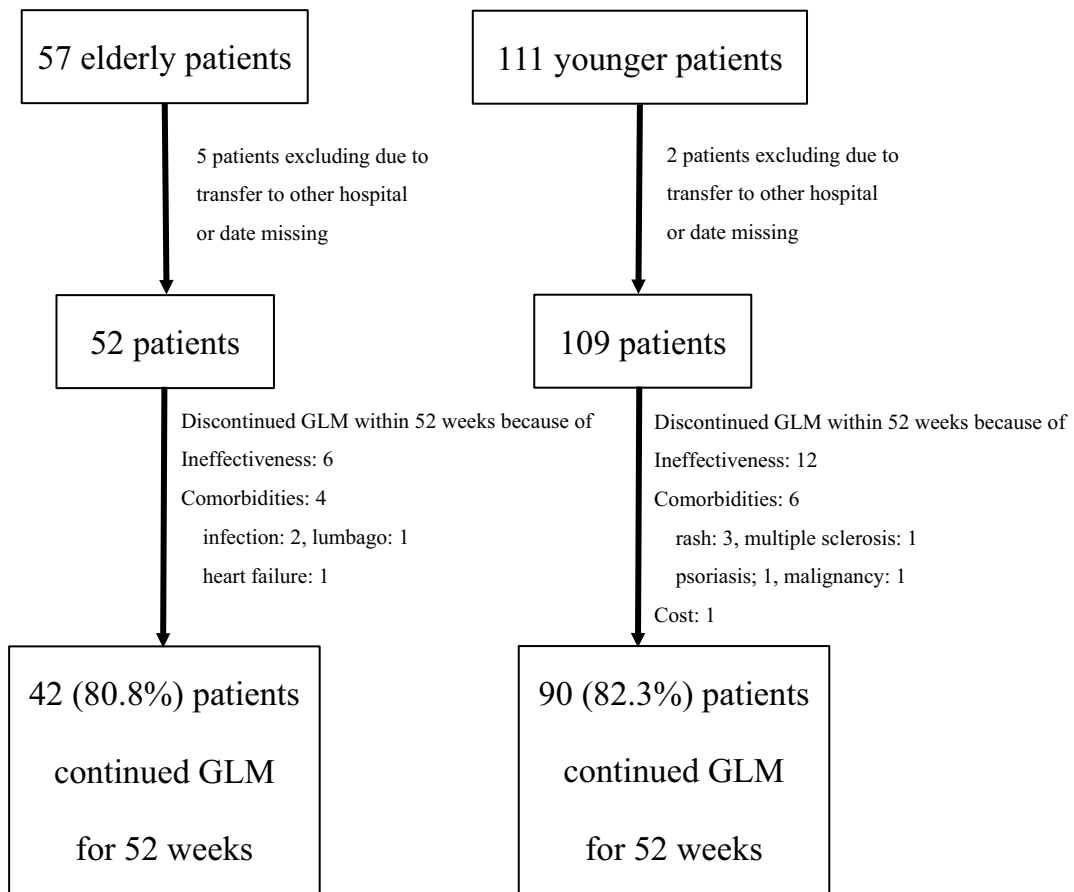


Figure 1. Numbers of patients in this study, reasons for golimumab (GLM) discontinuation within 52 weeks, and GLM survival rates over 52 weeks.

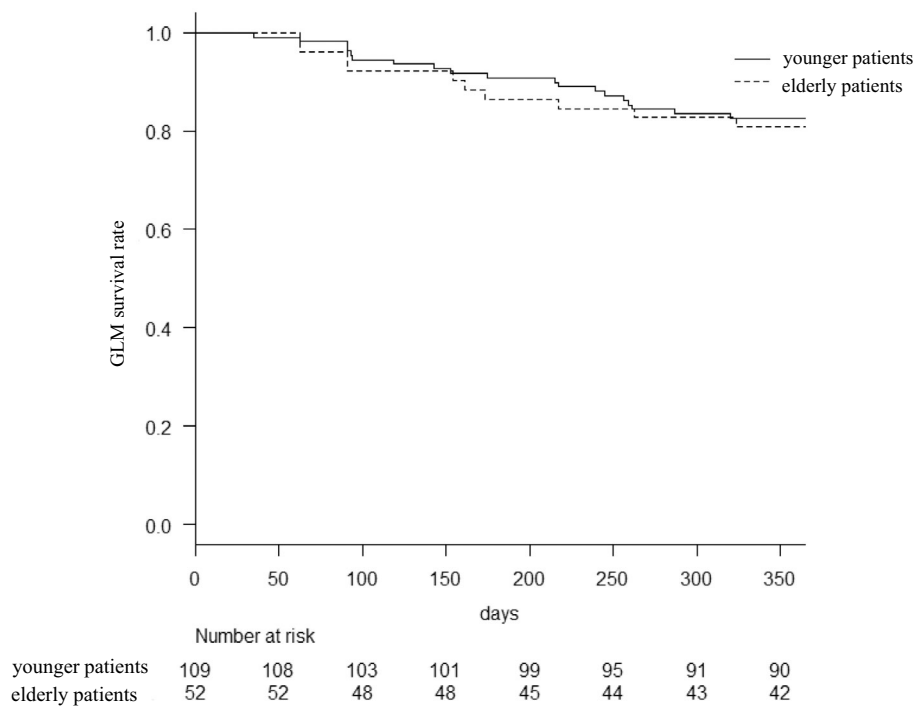


Figure 2. GLM survival rates in younger and elderly patients over 52 weeks, evaluated with the Kaplan-Meier method.

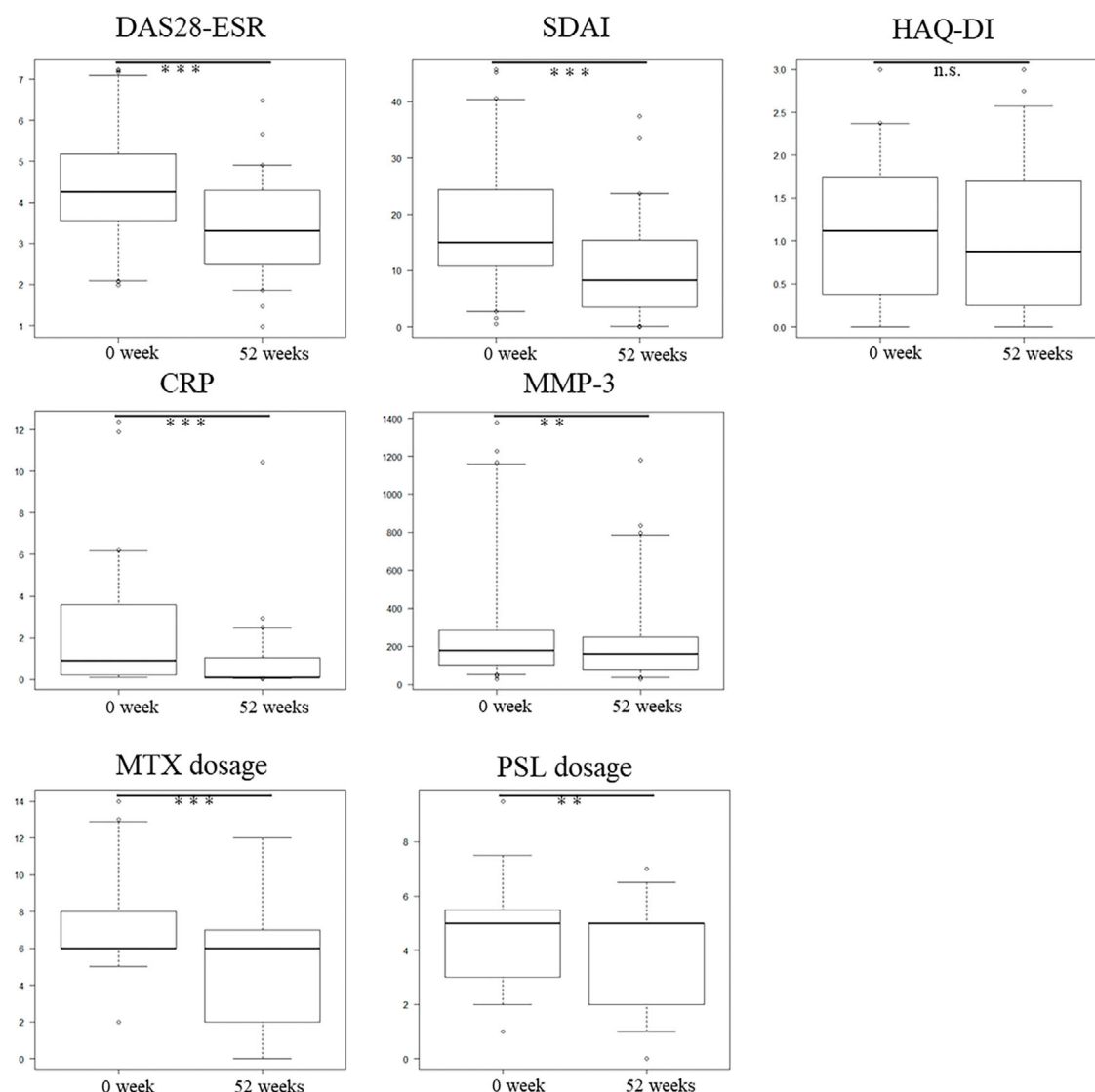


Figure 3. The comparison of patient characteristics at 0 and 52 weeks in elderly patients with rheumatoid arthritis who continued GLM for 52 weeks (n=42). *: p<0.05, **: p<0.01, ***: p<0.001

vs. 3.31 (2.50-4.29), p<0.001] and SDAI [14.9 (10.9-24.2) vs. 8.3 (3.5-15.1), p<0.001] were improved at 52 weeks. However, the HAQ-DI [1.12 (0.41-1.72) vs. 0.88 (0.25-1.71), p=0.694] did not change. The MMP-3 [178.1 (104.1-280.8) vs. 160.4 (75.2-241.6) ng/mL, p=0.008] and CRP [0.91 (0.20-3.44) vs. 0.11 (0.10-0.99) mg/dL, p<0.001] levels were significantly improved. The PSL [5.0 (3.0-5.5) vs. 5.0 (2.0-5.0) mg/day, p=0.014] and MTX [8 (6-8) vs. 6 (2-7) mg/week, p=0.007] dosages were significantly reduced.

The patient characteristics in the elderly group are shown in Table 2, stratified according to the MTX treatment status. The median age was significantly older among elderly patients without MTX than among elderly patients with MTX. The DAS28-ESR was also greater in elderly patients without MTX than in elderly patients with MTX [3.96 (3.40-4.63) vs. 4.76 (3.77-5.51), p=0.018]. There was no significant difference in the HAQ-DI, according to the MTX treatment status. The proportion of Steinbrocker class III/IV patients

was greater among those without MTX than among those with MTX. The eGFR and Ccr were significantly lower in patients without MTX than among those with MTX; the proportion of patients with an eGFR <60 mL/min/1.73 m² was significantly greater among patients without MTX than among those with MTX (60.0% vs. 14.8%, p=0.001). The proportion of patients treated with 100 mg GLM was significantly greater among patients without MTX than among those with MTX (18.5% vs. 56.0%, p=0.009). The proportions of patients using PSL and the dosage of PSL did not differ markedly between groups. The median MTX dosage among patients receiving MTX was 6 mg/week.

With respect to laboratory findings, the CRP level was greater in patients without MTX than in those with MTX. Conversely, the ESR, MMP-3, and rheumatoid factor levels did not differ markedly between groups. The proportions of patients with interstitial lung disease and amyloidosis were significantly greater among patients without MTX than among those with MTX. The GLM survival rates at 52

Table 2. Background of Elderly Patients with RA, Stratified according to MTX Status.

	With MTX (n=27)	Without MTX (n=25)	p value
Age (years old)	78 (76-80)	81 (78-82)	0.036
Sex (female, %)	81.5	80	1.000
DAS28-ESR	3.96 (3.40-4.63)	4.76 (3.77-5.51)	0.018
DAS28-CRP	3.49 (3.03-4.25)	4.19 (3.49-5.17)	0.025
CDAI	13.6 (9.5-17.9)	15.2 (11.2-25.4)	0.111
SDAI	13.9 (10.2-19.0)	21.5 (13.3-28.7)	0.060
HAQ-DI	1.12 (0.25-1.63)	1.13 (0.50-2.12)	0.601
TJC	2 (1-4)	4 (2-9)	0.004
SJC	3 (1-5)	1 (0-4)	0.182
EGA	30 (19-42)	47 (30-67)	0.003
PGA	43 (19-63)	48 (35-67)	0.128
Steinbrocker Stage I+II/III+IV (%)	33.3/66.7	32/68	1.000
Steinbrocker Class I+II/III+IV (%)	70.4/29.6	20/80	<0.001
Body Weight (kg)	50.7 (41.9-53.6)	47.3 (41.4-51.9)	0.564
Cr (mg/dL)	0.64 (0.53-0.71)	0.80 (0.60-0.97)	0.052
eGFR (mL/min/1.73m ²)	72.6 (62.0-84.5)	56.8 (43.9-71.8)	0.036
eGFR<60mL/min/1.73m ² (%)	14.8	60.0	0.001
Ccr (mL/min.)	58.8 (49.9-68.2)	44.2 (36.6-55.3)	0.012
Disease duration (years)	8 (6-23)	11 (3-20)	0.457
BIO naïve (%)	55.6	44.0	0.579
PSL usage (%)	70.4	80.0	0.528
PSL dosage (mg/day)	5.0 (3.0-5.0)	5.0 (4.5-6.6)	0.169
MTX dosage(mg/week)	6 (6-8)		
GLM dosage (100 mg, %)	18.5	56.0	0.009
CRP (mg/dL)	0.4 (0.1-1.9)	2.3 (0.7-3.7)	0.022
ESR (mm/hr)	28 (13-40)	51 (23-79)	0.124
MMP-3 (ng/mL)	163.0 (88.2-247.8)	267.2 (151.3-374.4)	0.066
RF (IU/L)	29 (8-71)	83 (17-112)	0.055
Anti-CCP antibody (U/mL)	22.1 (0.6-116.0)	113.0 (28.2-370.0)	0.015
Interstitial lung disease (%)	11	48	0.005
Bronchiectasis (%)	11	8	1.000
Amyloidosis (%)	0	16	0.047
Pleurisy (%)	0	4	0.481
Pericarditis (%)	4	0	1.000

DAS28-ESR: Disease Activity Score 28-erythrocyte sedimentation rate, DAS28-CRP: Disease Activity Score 28-C-reactive protein, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, HAQ-DI: Health Assessment Questionnaire Disability Index, TJC: tender joint count, SJC: swollen joint count, EGA: Evaluator's Global Assessment, PGA: Patient's Global Assessment, Cr: creatinine, eGFR: estimated glomerular filtration rate, Ccr: creatinine clearance, bDMARDs: biological disease-modifying anti-rheumatic drugs, PSL: prednisolone, MTX: methotrexate, GLM: golimumab, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, RF: rheumatoid factor, CCP: cyclic citrullinated peptide

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weeks were 76% in patients without MTX and 85% in patients with MTX ($p=0.413$). GLM was discontinued in patients without MTX because of ineffectiveness (3 patients, 12%), infection (two patients, 8%), and heart failure (1 patient, 4%). GLM was discontinued in patients with MTX because of ineffectiveness (3 patients, 11%) and lumbago (1 patient, 4%).

Table 3 shows the comparison of disease activities, treatments, and laboratory findings between 0 and 52 weeks of GLM treatment, stratified according to the MTX treatment

status. DAS28-ESR and SDAI were improved at 52 weeks in both groups (DAS28-ESR in patients with and without MTX: $p<0.001$ and $p=0.026$, respectively; SDAI in patients with and without MTX: $p<0.001$ and $p=0.003$, respectively). The HAQ-DI was not improved in either group (patients with and without MTX: $p=0.293$ and $p=0.619$, respectively). The PSL dosage also was not reduced in either group, and only one patient in the group with MTX was able to discontinue PSL. The MTX dosage was decreased in 13 patients with MTX; among these, 4 discontinued MTX altogether.

Table 3. Comparison of Patient Characteristics at 0 and 52 Weeks after Initiation of GLM Treatment.

	With MTX (n=23)			Without MTX (n=19)		
	0 week	52 weeks	p value	0 week	52 weeks	p value
Age (years old)	78 (76-80)			81 (77-82)		
Sex (female, %)	82.6			78.9		
DAS28-ESR	3.82 (3.40-4.52)	2.68(2.34-3.56)	<0.001	4.76 (3.94-5.46)	4.25 (3.23-4.59)	0.026
DAS28-CRP	3.41 (2.79-4.19)	2.14(1.57-2.84)	<0.001	4.19 (3.46-5.13)	3.48 (2.47-4.03)	0.001
CDAI	12.6 (8.2-17.9)	7.0 (3.3-11.0)	0.002	16.0 (9.6-24.8)	12.9 (4.8-17.9)	0.014
SDAI	13.9 (9.2-18.5)	7.2 (3.4-11.0)	<0.001	21.5 (11.6-28.4)	13.8 (5.9-19.3)	0.003
HAQ-DI	1.13 (0.25-1.63)	0.63 (0.25-1.44)	0.293	1.12 (0.56-1.94)	1.25 (0.41-2.06)	0.619
TJC	2 (1-3)	1 (0-2)	0.100	3 (2-11)	2 (0-4)	0.101
SJC	3 (1-5)	0 (0-2)	<0.001	1 (0-4)	0 (0-2)	0.665
EGA	30 (17-35)	10 (5-29)	0.016	50 (27-67)	30 (19-46)	0.011
PGA	40 (17-67)	21 (4-48)	0.024	58 (35-69)	45 (19-55)	0.012
Steinbrocker Stage I+II/III+IV (%)	26.1/ 73.9			26.3/ 73.7		
Steinbrocker Class I+II/III+IV (%)	69.6/ 30.4			15.8/ 84.2		
Body Weight (kg)	50.7 (43.6-53.2)			44.6 (41.8-51.8)		
Cr (mg/dL)	0.64 (0.54-0.71)			0.80 (0.59-1.06)		
eGFR (mL/min/1.73m ²)	72.6 (63.4-84.5)			56.8 (42.2-79.3)		
Ccr (ml/min.)	58.1 (49.9-67.4)			43.8 (35.9-58.4)		
Disease duration (years)	13 (7-26)			14 (5-21)		
BIO naïve (%)	56.5			52.6		
PSL usage (%)	65.2	60.9	1.000	73.7	73.7	1.000
PSL dosage (mg/day)	5.0 (3.0-5.0)	4.0 (1.8-5.0)	0.050	5.0 (3.5-6.9)	5.0 (2.8-5.8)	0.139
MTX dosage (mg/week)	6 (6-8)	6 (2-7)	0.007	0 (0-0)		
GLM dosage (100mg, %)	17.4			47.4		
CRP (mg/dL)	0.40 (0.10-1.20)	0.10 (0.01-0.16)	0.001	2.00 (0.50-3.65)	0.86 (0.15-1.85)	0.013
ESR (mm/hr)	28 (14-40)	17 (9-23)	0.003	38 (23-73)	36 (14-52)	0.286
MMP-3 (ng/mL)	163.0 (88.2-247.8)	125.3 (61.9-193.7)	0.135	199.3 (128.1-314.0)	183.4 (79.7-307.3)	0.026
RF (IU/L)	20 (7-67)	13 (8-61)	0.218	81 (13-157)	17 (12-112)	0.107
Anti-CCP antibody (U/mL)	15.5 (0.6-101.2)			113.0 (42.6-489.5)		

DAS28-ESR: Disease Activity Score 28-erythrocyte sedimentation rate, DAS28-CRP: Disease Activity Score 28-C-reactive protein, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, HAQ-DI: Health Assessment Questionnaire Disability Index, TJC: tender joint count, SJC: swollen joint count, EGA: Evaluator's Global Assessment, PGA: Patient's Global Assessment, Cr: creatinine, eGFR: estimated glomerular filtration rate, Ccr: creatinine clearance, bDMARDs: biological disease-modifying anti-rheumatic drugs, PSL: prednisolone, MTX: methotrexate, GLM: golimumab, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, RF: rheumatoid factor, CCP: cyclic citrullinated peptide

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The CRP level was significantly improved in both groups (patients with and without MTX: $p=0.001$ and $p=0.013$, respectively); however, the MMP-3 level was improved only in patients without MTX (patients with and without MTX: $p=0.135$ and $p=0.026$, respectively).

Discussion

In this study, we evaluated the effectiveness and safety of GLM, primarily in elderly patients. First, we found that the GLM survival rates over 52 weeks were 80.8% in elderly patients and 82.3% in younger patients. Second, in elderly patients with RA, disease activities (DAS28-ESR and SDAI) and laboratory findings (CRP and MMP-3) significantly improved as a result of GLM treatment, while dosages of MTX and PSL significantly decreased. However, the HAQ-DI did not improve. Third, disease activities improved in elderly patients with RA, regardless of MTX treatment

status.

To evaluate the effectiveness and safety of GLM in elderly patients, we investigated the patient characteristics and course of treatment among individuals who had been treated with GLM in our hospital. Disease activities were similar in elderly and younger patients. Conversely, the distribution of Steinbrocker classes (19) indicated that elderly patients had worse activities of daily living (ADL) than younger patients. Furthermore, the creatinine, eGFR, and Ccr values were worse in elderly patients than in younger patients. These findings are consistent with previous reports (4, 5). In particular, MTX use was less common and the MTX dosage lower in elderly patients than in younger patients. Overall, the renal function was worse in elderly patients than in younger patients (4, 5). Therefore, the MTX dosage was lower in this population, and MTX sometimes could not be used for treatment in elderly patients (21). The MMP-3 level might also be affected by the poor renal function in elderly

patients (22).

The GLM survival rate at 52 weeks was 80.8% in elderly patients; this was not significantly different from the GLM survival rate in younger patients. In previous reports, the GLM survival rate at 52 weeks was $\leq 80\%$ in elderly patients (defined as ≥ 60 or ≥ 65 years old) (23-25). In contrast to the results of previous studies, we found that the GLM survival rate did not considerably differ according to age, despite the older definition of elderly being used in our study. Okazaki et al. reported that the GLM survival rate was significantly higher in younger patients than in elderly patients because of discontinuation at four weeks (16). By the fourth week, the factors that significantly differed between elderly and younger patients were patient selection and hospital transfer. Comorbidities, disease progression, and adverse events did not influence the difference in the GLM survival rate. The survival rate may have been higher in our study because it was performed a few years after the study by Okazaki et al.; furthermore, we were proficient in using GLM and guiding patient selection, resulting in less frequent early withdrawal. In six and two elderly patients in our study, GLM was discontinued because of ineffectiveness and infection, respectively. According to the British Society for Rheumatology guideline (26), etanercept and abatacept are recommended for use in patients at high risk of infection. Our findings suggest that GLM may also be safe for use in patients at high risk of infection.

In our study, the HAQ-DI among elderly patients was not improved after 52 weeks of GLM treatment. Conversely, younger patients exhibited improvements of disease activities, laboratory findings, and HAQ-DI (data not shown). The HAQ-DI might not have improved in elderly patients because they originally had worse ADL than younger patients because of their comorbidities (e.g., osteoarthritis, osteoporosis, and lumbar canal stenosis). Thus, although the elderly patients experienced improvements in disease activities, their overall ADL statuses did not improve. Our findings concerning the improvement of HAQ-DI in elderly patients compared with younger patients were similar to the results reported by Radovits et al. (27). Genevay et al. also reported that HAQ-DI outcomes were better in younger patients with RA than in elderly patients with RA; they found that elderly patients had more comorbidities, including osteoarthritis (25). Both the MTX and PSL dosages were reduced in elderly patients at 52 weeks. A reduction in the PSL dosage is preferable for preventing PSL-related side effects (e.g. infection) (7, 28); our results suggest that the initiation of GLM may aid in avoiding PSL-related side effects.

In summary, GLM can be used safely and effectively in elderly patients. The survival rate in this study was similar to the rates in previous reports, in which elderly patients were defined as those ≥ 60 or ≥ 65 years old.

In the present, we found that elderly patients without MTX had a worse renal function than those without MTX; furthermore, 60% of patients without MTX had an eGFR < 60 mL/min/1.73 m². This low eGFR contributed to the

avoidance of MTX treatment in some patients. As a result, 100 mg GLM was used in more patients without MTX than in patients with MTX. The DAS28-ESR value and anti-cyclic citrullinated peptide antibody titers were greater in patients without MTX than in those with MTX. The proportion of patients with Steinbrocker classes III and IV was greater among patients without MTX than among those with MTX. These data suggested that patients without MTX had worse ADL and included a greater proportion of frail patients than those with MTX; furthermore, patients without MTX were presumed to have a worse prognosis with respect to their joints than those with MTX. Because patients without MTX had a greater disease activity, worse ADL, and higher anti-cyclic citrullinated peptide antibody titer than those with MTX, their courses of treatment were difficult. However, as mentioned above, the GLM survival rate over 52 weeks was good in elderly patients. Furthermore, disease activities (e.g. DAS28-ESR and SDAI) were improved at 52 weeks in elderly patients, regardless of MTX status, and the CRP and MMP-3 levels were also improved. Despite treatment difficulty, the use of 100 mg GLM alone contributed to improvements in disease activities in patients who were unable to receive MTX treatment. Nonetheless, the HAQ-DI did not improve in either group of elderly patients. Overall, the disease activities and laboratory findings were improved in elderly patients, regardless of MTX status, although their ADL did not change. These findings suggest that GLM is useful for elderly patients with and without MTX, but it does not contribute to improvements in the HAQ-DI in either subset of patients.

Several limitations associated with the present study warrant mention. First, it was performed in a single institution. Second, the initiation and discontinuation of GLM were determined by the rheumatologist for each patient; there were no established guidelines for discontinuation of GLM. To more extensively characterize GLM survival rates, a multicenter study with a fixed protocol is needed.

In our study, GLM was effective for both younger and elderly patients, regardless of concurrent MTX treatment. Okazaki et al. previously reported the GLM survival rate in patients ≥ 75 years old with RA (16), but their observation period was limited to 24 weeks. To our knowledge, our study is the first investigation of the 52-week GLM survival rate in patients ≥ 75 years old with RA. Our findings affirm the use of GLM in elderly patients, regardless of MTX status. In the European League Against Rheumatism guideline (7), patients with RA who cannot receive MTX are recommended to undergo IL-6 inhibitor treatment, instead of tumor necrosis factor inhibitor treatment. Our results indicate that GLM can serve as an alternative option for elderly patients with RA who cannot receive MTX.

Author's disclosure of potential Conflicts of Interest (COI).

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