Original article

Comparison of golimumab 100 mg monotherapy to golimumab 50 mg plus methotrexate in patients with rheumatoid arthritis: Results from a multicenter, cohort study

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Abstract

Objective: The aim of this study was to compare the efficacy and safety of golimumab (GLM) 50 mg + methotrexate (MTX) combination therapy and GLM 100 mg monotherapy in patients with rheumatoid arthritis (RA).

Methods: The subjects were 115 RA patients (92 females, 23 males; median (range) age 64 (17-87) years; median (range) disease duration 8 (0.6-48) years) started on GLM. Eighty-three patients received GLM 50 mg/4 weeks + MTX (C group; median (range) MTX dosage 8 (2-16) mg/week), and 32 patients received GLM 100 mg/4 weeks (M group).

Serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3, disease activity score (DAS) 28-ESR, DAS28-CRP, simplified disease activity index, and clinical disease activity index were evaluated 4, 12, and 24 weeks after starting GLM.

Results: There were no significant differences in disease activity, adverse events, and drug continuation rates at 24 weeks between the groups. The DAS28-ESR remission rate was 34% in the C group and 26% in the M group.

Conclusions: GLM 100 mg monotherapy improved disease activity as well as GLM 50 mg + MTX combination therapy. GLM 100 mg monotherapy appears to have a sufficient therapeutic effect in RA patients who cannot take MTX.

Introduction

The treatment of rheumatoid arthritis (RA) has been transformed by the development of novel agents targeting biological factors [1, 2], and the idea of “treat to target” has emerged [3]. Early aggressive treatment with methotrexate (MTX) and tumor necrosis factor inhibitors can lead to clinical, radiological, and even functional remission in a large proportion of patients with RA [4-6]. However, some patients cannot use MTX due to conditions such as respiratory, liver, kidney, and blood diseases, and previous studies reported that the treatment effect of TNF inhibitors diminishes without concomitant use of MTX [6].

Golimumab (GLM) is a human monoclonal antibody specific for human TNF-α, and it is indicated in RA patients with moderate to severe disease activity [7-9]. This drug was introduced in 2011 in Japan, the only country that currently allows a dosage of 100 mg per 4 weeks. GLM not only exhibits enhanced therapeutic effects with concomitant MTX use [10-12], but it also shows efficacy when used alone as monotherapy, especially at 100 mg [13]. However, few papers have so far compared GLM 50 mg + MTX with GLM 100 mg monotherapy in clinical settings.

The aim of this study was to compare the efficacy and safety of GLM 50 mg + MTX combination therapy and GLM 100 mg monotherapy in patients with RA.

Patients and Methods

Patients

The Gunma Rheumatoid Arthritis Network (GRN) is a multicenter, observational study of RA patients at Gunma University Hospital and four other institutes. The ethics committee of Gunma University approved the protocol for this study (Approval No.23-37). The subjects were 115 RA patients (92 females; 23 males) who started receiving GLM treatment from September 2011 to May 2013 at the GRN. Inclusion was based on a clinical diagnosis of RA according to the 2010 American College of Rheumatology/European League against Rheumatism classification criteria [14] and insufficient response to previous anti-rheumatic drugs. Patients with other inflammatory diseases, previous administration of GLM, demyelinating disease, congestive heart failure, active tuberculosis, or other active infectious diseases were excluded. The median age (range) of the patients was 64 years (17–87 years), and the median disease duration was 8 years (0.6–48 years). Seventy-two of the 115 patients were bio-naïve patients. Eighty-three patients received GLM 50 mg/4 weeks + MTX as combination therapy (C group), and 32 patients received GLM 100 mg/4 weeks as monotherapy (M group). The median MTX dosage in the GLM 50 mg/4 weeks + MTX group was 8 (2-16) mg/week.

The GLM dose was 50 mg in patients who could take MTX and 100 mg in patients who could not take MTX. The dose increases or decreases of GLM during the study were determined at the discretion of each

physician; the clinical data of these patients were included in the analysis.

Clinical assessment of serum markers

The RA status was evaluated 4, 12, and 24 weeks after the initiation of GLM treatment with the serum C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and level of matrix metalloproteinase (MMP)-3 as markers of inflammation and cartilage degradation. The disease activity score (DAS) 28-ESR, DAS28-CRP, simplified disease activity index (SDAI), and clinical disease activity index (CDAI) were used to evaluate RA disease activity [15-17]. The DAS28 was calculated according to the standard formula, and disease activity was classified as follows: DAS28-ESR > 5.1, high disease activity (HDA); 3.2 – 5.1, moderate disease activity (MDA); < 3.2, low disease activity (LDA); and < 2.6, remission [15]. The GLM continuation rates at 24 weeks were also examined, and specific adverse events that may be associated with GLM as judged by each physician were also evaluated.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 21 software (International Business Machines Corp., Armonk, NY, USA); a P value < 5% was considered significant. Chi-square tests were used for comparisons between the two groups for categorical variables, and Mann-Whitney U-tests were used to assess continuous variables. The log-rank test was used to compare the drug continuation rates

between the two groups. The last observation carried forward (LOCF) method was used to assess the patients who discontinued GLM therapy [18].

Results

The patients' characteristics (n=115) are shown in Table 1.

Table 2 shows a comparison between the C group and the M group. The M group was older than the C group, had a smaller percentage of bio-naïve patients, and had a greater number of patients with advanced joint destruction. However, there were no significant differences in serum markers or disease activity between the groups at baseline. In 5 of 83 patients in the C group, GLM was increased to 100 mg/4 weeks due to lack of effectiveness. GLM was not decreased in any of the patients in the M group. There were no patients who switched from the M group to the C group or the C group to the M group during this study period.

Serum markers and RA disease activity were evaluated for 24 weeks. The DAS28-ESR classification of disease activity showed no significant differences between the two groups at baseline and 24 weeks after treatment. While DAS28-CRP at week 12 and CDAI at week 4 were significantly lower in the C group than in the M group, there were no significant differences between the two groups at 24 weeks (Table 3). The tender joint count of 28 joints and the patient global visual analogue scale were significantly lower in

the M group at week 4 (p=0.02, p=0.01). However, the swollen joint count of 28 joints and the patient global visual analogue scale were not significantly different between the 2 groups at each point.

The DAS28-ESR remission (DAS28-ESR < 2.6) rate was 34% in the C group and 26% in the M group (Figure 1).

Seventeen patients in the C group and 5 patients in the M group discontinued GLM therapy by 24 weeks. The GLM continuation rate at 24 weeks was 80% in the C group and 84% in the M group (Figure 2).

Adverse events developed in 6 of 83 patients in the C group, and GLM administration was discontinued in 4 patients. Adverse events included generalized itchiness, high KL-6 level, pneumonia, injection site reaction, decreased platelets, and cough, with each event occurring in one patient. Adverse events developed in 3 of 32 patients in the M group, and GLM administration was discontinued in one patient. Adverse events included gastric ulcer, high KL-6 level, and herpes zoster, with each event occurring in one patient. No significant differences were observed between the two groups in the incidence of adverse events.

Discussion

This is the first study that directly compared GLM 100 mg monotherapy with GLM 50 mg + MTX therapy in clinical settings. With regards to the efficacy of GLM 100 mg with concomitant MTX use in

RA patients, Keystone et al. [10] and Tanaka et al. [12] reported that both GLM 50 mg and 100 mg were effective. In contrast, Takeuchi et al. reported that GLM 100 mg showed a significantly greater efficacy than 50 mg in patients who did not concurrently use MTX. In daily clinical practice, Sato et al. [19] reported that GLM 50 mg (n=43), GLM increased from 50 mg to 100 mg (n=23), and GLM 100 mg (n=8) were all effective at 52 weeks. However, there were only six patients who used GLM 100 mg without MTX, and a sufficient between-group comparison has not been conducted. Kanbe [20] et al. reported that the total Sharp score was significantly better in the GLM 100-mg group than in the 50-mg group after 24 weeks in clinical practice. In the present study, there were no significant differences in disease activity for 24 weeks between GLM 100 mg monotherapy and GLM 50 mg + MTX therapy. However, DAS28-CRP at week 12, CDAI at week 4, tender joint counts at week 4, and the patient global visual analogue scale at week 4 were significantly lower in the C group than in the M group. These results suggest that GLM 50 mg plus MTX therapy has a faster therapeutic effect than GLM 100-mg monotherapy. The progression of joint destruction was not assessed in the present study; thus, the differences in joint destruction could not be determined.

Tanaka et al. [12] reported in Japanese RA patients that anti-GLM antibody did not appear in a 52-week investigation with either GLM dose, 50 mg or 100 mg, when concomitantly treated with MTX. Takeuchi et al. [13] demonstrated that anti-GLM antibody appeared in 3.2% and 4.0% of Japanese RA patients who were given GLM monotherapy at 50 mg and 100 mg, respectively, for 24 weeks. Thus, it is

considered that concurrent use of MTX with GLM not only facilitates the effects of MTX as an antirheumatic drug, but also suppresses the appearance of anti-GLM antibody. However, GLM antibody was not assessed in this study, so that it is unclear whether GLM antibody was related to the therapeutic effects of GLM in the C group,

Although adverse events such as infections are a concern with biological agents such as GLM, relatively few reports compared the occurrence of adverse events between different biological agents. In a meta-analysis, GLM was reported to have a lower risk of adverse events than abatacept, rituximab, and tocilizumab [21]. Adverse events also occurred in 6 of 83 patients in the C group and in 3 of 32 patients in the M group, although none of them were serious conditions requiring hospitalization, and no significant differences between the two groups were observed.

Smolen et al. [22] used GLM in patients who had previously used TNF inhibitors, and they reported that, compared to placebo, GLM was effective in patients who used one or two TNF inhibitors in prior treatment. However, GLM was not effective in patients who used 3 or more TNF inhibitors in prior treatment. Mancarella et al [23] and Burmester et al [24] stated that younger age was a predictor of TNF inhibitor treatment inducing remission or low disease activity. In addition, Heijde et al [25] reported that a lower level of joint destruction at baseline predicts remission with etanercept treatment. In the present study, a very large proportion (81%) of the M group previously used other biological agents; in fact, 11 of 32 patients previously used 3 or more biological agents. Furthermore, patients were older in the M group

than in the C group, and more patients in the M group had advanced joint destruction. Nonetheless, favorable improvements in disease activity and high drug continuation rates were observed in these patients with GLM 100-mg monotherapy.

There are several limitations to this study. The first is that the progression of joint destruction on plain X-ray was not evaluated, and activities of daily living were not assessed. The second limitation is that this study was an observational study of actual clinical practice, and patient selection was dependent on the use of MTX; hence, the patients' background characteristics differed between the two groups. The third is that the study population was small, consisting of 115 patients. Finally, the fourth is that the observation period was short (24 weeks), and long-term efficacy remains unknown. In order to elucidate the above points, results from a long-term, large-scale study would be needed.

In conclusion, GLM 100 mg monotherapy improved disease activity as well as GLM 50 mg + MTX combination therapy. These results suggest that GLM 100 mg monotherapy has a sufficient therapeutic effect in RA patients who cannot use MTX in clinical practice.

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Conflict of interest statement

None

References

1. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64:625-39. doi: 10.1002/acr.21641.

2. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492-509. doi: 10.1136/annrheumdis-2013-204573. Epub 2013 Oct 25.

3. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al; for the T2T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631-7. doi: 10.1136/ard.2009.123919. Epub 2010 Mar 9.

4. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group (IFX XP). Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000;343:1594-602.

5. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group (IFX HAQ). Sustained

improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004;50:1051-65.

6. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363:675-81.

5. Favalli EG, Biggioggero M, Meroni PL. Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an “anchor” drug? Autoimmun Rev. 2014;13:1102-8. doi: 10.1016/j.autrev.2014.08.026. Epub 2014 Aug 26.

6. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab + methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26-37.

7. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III,

multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009;60:2272-83. doi: 10.1002/art.24638.

8. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008;58:964-75. doi: 10.1002/art.23383.

9. Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010;62:917-28. doi: 10.1002/art.27348.

10. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al; GO-FORWARD Study. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009;68:789-96. doi: 10.1136/ard.2008.099010. Epub 2008 Dec 9.

11. Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis. 2010;69:1129-35. doi: 10.1136/ard.2009.116319. Epub 2010 May 5.

12. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al; GO-FORTH Study

Group. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012;71:817-24. doi: 10.1136/ard.2011.200317. Epub 2011 Nov 25.

13. Takeuchi T, Harigai M, Tanaka Y, Yamanaka H, Ishiguro N, Yamamoto K, et al; GO-MONO study group. Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks. Ann Rheum Dis. 2013;72:1488-95. doi: 10.1136/annrheumdis-2012-201796. Epub 2012 Sep 14.

14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81. doi: 10.1002/art.27584.

15. DAS SCORE.NL, http://www.das-score.nl/, the Netherlands

16. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005;23:S100-8.

17. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003;42:244-57.

18. Mallinckrodt CH, Sanger TM, Dubé S, DeBrota DJ, Molenberghs G, Carroll RJ, et al. Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. Biol Psychiatry. 2003;53:754-60.

19. Sato E, Tanaka E, Nakajima A, Inoue E, Shimizu Y, Yamaguchi R, et al. Assessment of the effectiveness of golimumab 50-mg and 100-mg regimens in patients with rheumatoid arthritis in daily practice. Mod Rheumatol. 2015 9:1-6. [Epub ahead of print]

20. Kanbe K, Chiba J, Inoue Y, Taguchi M, Yabuki A. Predictive factors related to the efficacy of golimumab in patients with rheumatoid arthritis. Clin Med Insights Arthritis Musculoskelet Disord. 2015 19;8:25-32. doi: 10.4137/CMAMD.S22155. eCollection 2015.

21. Schoels M, Aletaha D, Smolen JS, Wong JB. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor α inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis. Ann Rheum Dis. 2012;71:1303-8. doi: 10.1136/annrheumdis-2011-200490. Epub 2012 Jan 30.

22. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;18;374:210-21. doi: 10.1016/S0140-6736(09)60506-7. Epub 2009 Jun 26.

23. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D J, et al; Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. Rheumatol. 2007;34:1670-3. Epub 2007 Jul 1.

24. Burmester GR, Ferraccioli G, Flipo RM, Monteagudo-Sáez I, Unnebrink K, Kary S, et al; Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2008; 15;59:32-41. doi: 10.1002/art.23247.

25. van der Heijde D, Klareskog L, Landewé R, Bruyn GA, Cantagrel A, Durez P, et al; Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007;56:3928-39.

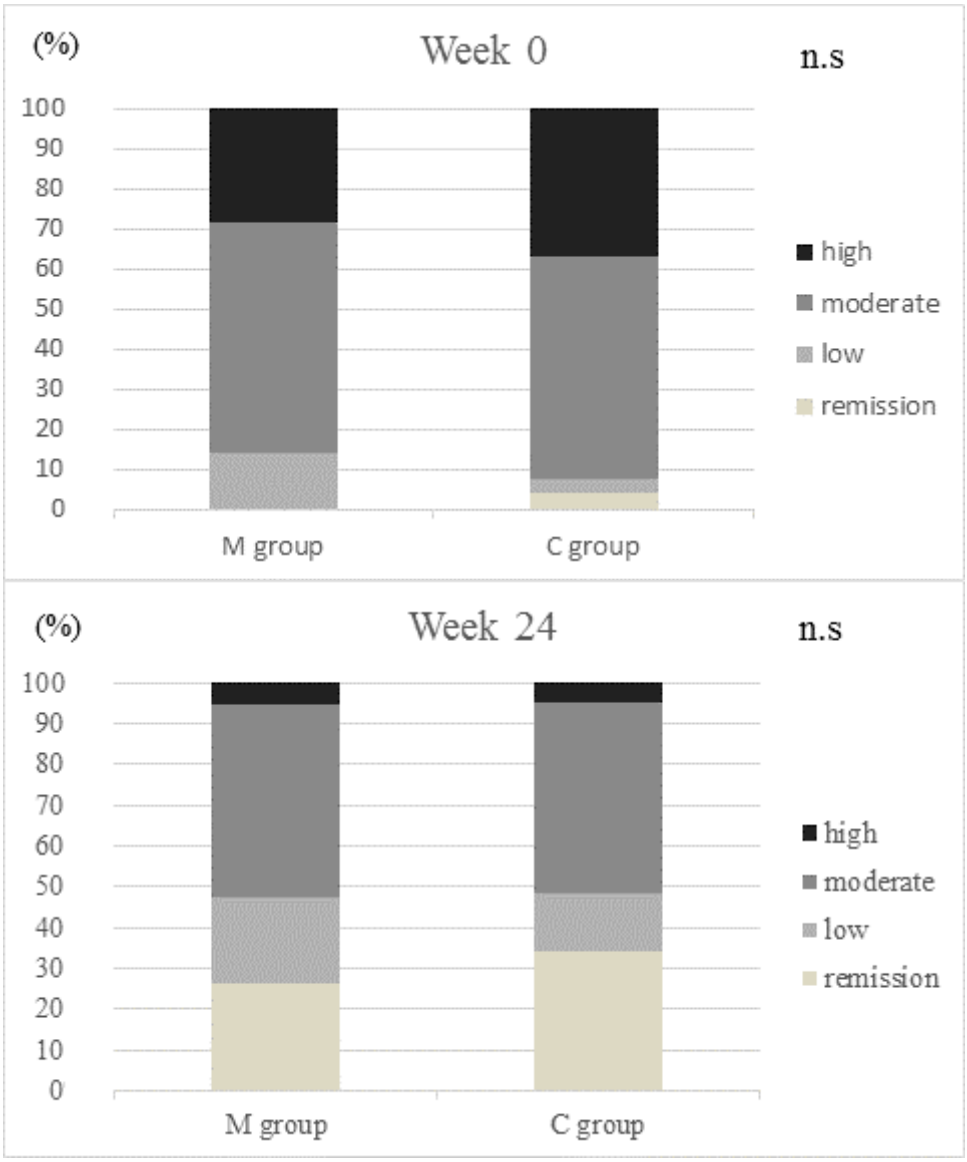

Figure 1. DAS28-ESR before treatment and at week 24 in each group

The DAS28-ESR disease activity classification shows no significant differences between the two groups before treatment (a) and at week 24 (b). (Chi-square test)

C group: GLM 50 mg/4 weeks + MTX group

M group: GLM 100 mg/4 weeks as monotherapy group

DAS28-ESR: disease activity score 28-erythrocyte sedimentation rate, GLM: golimumab, MTX:

methotrexate, n.s: not significant

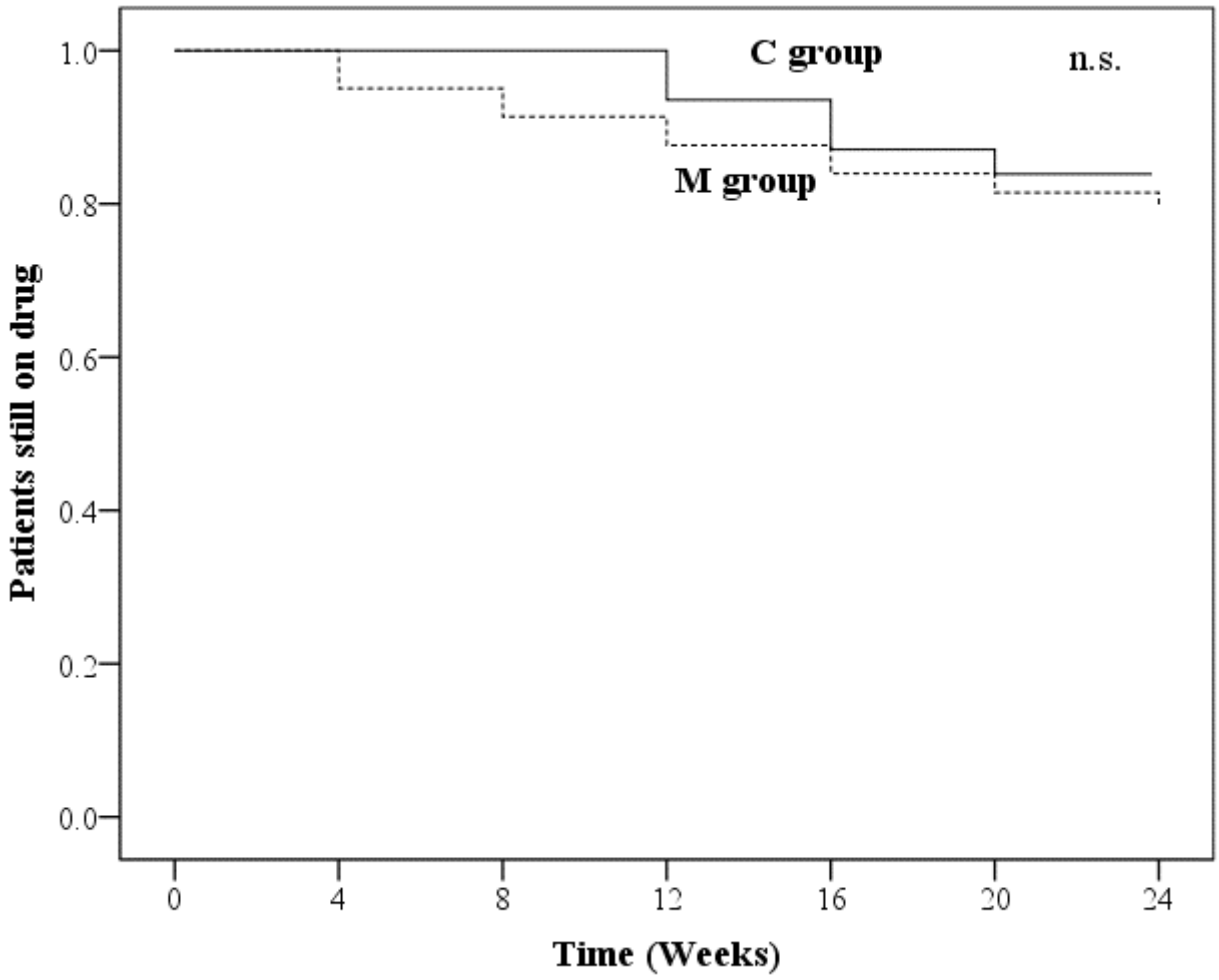

Figure 2. Drug continuation rate of GLM

The drug continuation rate to week 24 shows no significant difference between the two groups. (Log-rank test)

C group: GLM 50 mg/4 weeks + MTX group

M group: GLM 100 mg/4 weeks as monotherapy group

GLM: golimumab, MTX: methotrexate, n.s: not significant

Table 1. Patients' backgrounds characteristics

	n = 115
Age (years)	66.5 (17-87)
Sex, male (%)	4
Disease duration (years)	8.0 (0.6-48.0)
Steinbrocker Stage (I/II/III/IV)	5/23/15/72
Steinbrocker Class (1/2/3/4)	16/77/22/0
Bio-naïve (%)	37
Concomitant MTX (%)	72
MTX dosage (mg/week)	8.0 (2.0-16.0)
Concomitant PSL (%)	50
PSL dosage (mg/day)	5.0 (1.0-10.0)
CRP (mg/dL)	1.45 (0.00-13.29)
ESR (mm/h)	40 (3-130)
MMP-3 (ng/mL)	197.6 (19.2-1278.6)
RF positive (%)	82
ACPA positive (%)	81
DAS28-ESR	4.65 (2.28-7.97)

DAS28-CRP	3.53 (0.99-6.37)
SDAI	21.2 (0.4-63.7)
CDAI	18.7 (0.3-62.0)

Median (range)

MTX: methotrexate, PSL: prednisolone, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, DAS: disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index

Table 2. Characteristics of the patients in the two groups

	C group (n=83)	M group (n=32)	p*
Age (years)	64 (17-87)	70 (55-77)	0.03
Gender, male (%)	2	3	0.83
Disease duration (years)	8 (1-47)	8 (2-48)	0.49
Steinbrocker Stage (I/II/III/IV)	5/21/12/45	0/2/3/27	0.02
Steinbrocker Class (1/2/3/4)	14/53/16/0	2/24/6/0	0.31
Bio-naïve (%)	45	19	0.01
The number of previous biologics (0/1/2/3/4/5)	36/24/18/3/1/1	6/8/7/5/6/0	<0.01
Concomitant MTX (%)	100	0	<0.01
MTX dosage (mg/week)	8 (2-16)	0 (0-0)	<0.01
Concomitant PSL (%)	39	57	0.16
PSL dosage (mg/day)	3 (1-10)	5 (0.5-10)	0.29
RF positive (%)	81	84	0.44
ACPA positive (%)	78	87	0.20
Treatment for latent tuberculosis (%)	2	0	0.52
CRP (mg/dl)	1.41 (0.02-13.12)	1.20 (0.00-10.29)	0.72
ESR (mm/h)	42 (3-130)	38 (4-112)	0.35
MMP-3 (ng/ml)	195.6 (20.8-1086.3.5)	199.5 (19.2-1278.6)	0.15
Tender joint count (0-28)	3 (0-25)	3 (0-28)	0.97
Swollen joint count (0-28)	3 (0-24)	3 (0-10)	0.47
Patient's global visual analogue scale (cm)	5.0 (0.0-9.0)	6.0 (1.0-10.0)	0.16
Evaluator's global visual analogue scale (cm)	5.0 (0.3-9.0)	5.0 (1.5-9.0)	0.80
DAS28-ESR	4.70 (2.28-7.97)	4.54 (2.90-7.96)	0.57
DAS28-CRP	3.60 (0.99-6.18)	3.42 (2.07-6.37)	0.92
SDAI	21.1 (0.4-62.2)	20.4 (5.6-63.7)	0.93
CDAI	19.0 (0.3-62.0)	18.0 (4.0-57.3)	0.72

*Chi-square test for dichotomous variables and Mann-Whitney test for continuous variables

Median (range)

C group: GLM 50 mg/4 weeks + MTX group

M group: GLM 100 mg/4 weeks group

GLM: golimumab, MTX: methotrexate, PSL: prednisolone, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, DAS: disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index

Table 3. Clinical course of GLM therapy

		Week 4	p*	Week 12	p*	Week 24	p*
CRP (mg/dL)	C group	0.51 (0.00-7.18)	0.73	0.42 (0.00-8.75)	0.19	0.45 (0.00-7.18)	0.76
	M group	0.68 (0.01-14.77)		0.88 (0.01-6.92)		0.52 (0.01-7.03)	
ESR (mm/h)	C group	26 (4-118)	0.53	28 (2-115)	0.30	25 (2-111)	0.67
	M group	31 (5-122)		32 (4-123)		26 (5-123)	
MMP-3 (ng/mL)	C group	187.7 (10.7-1118.3)	0.86	142.1 (16.3-735.6)	0.46	122.6 (18.3-1093.9)	0.78
	M group	187.0 (19.7-1639.4)		122.8 (23.0-729.4)		107.5 (15.3-593.0)	
DAS28-ESR	C group	3.76 (1.05-8.08)	0.05	3.33 (0.56-6.19)	0.12	3.38 (0.49-6.47)	0.97
	M group	4.29 (2.46-7.43)		3.88 (1.50-6.24)		3.11 (1.67-6.14)	
DAS28-CRP	C group	2.78 (1.00-6.27)	0.59	2.32 (0.98-4.64)	0.04	2.51 (0.97-4.99)	0.94
	M group	3.09 (1.72-6.10)		2.84 (1.13-4.59)		2.29 (1.26-448)	
SDAI	C group	14.5 (0.2-58.8)	0.10	9.5 (0.3-33.8)	0.18	9.5 (0.0-40.3)	0.41
	M group	17.1 (5.0-60.0)		12.3 (1.3-28.9)		10.1 (2.8-28.9)	
CDAI	C group	12.0 (0.1-57.5)	0.03	8.2 (0.1-28.0)	0.12	9.0 (0.0-36.5)	0.25
	M group	15.3 (4.3-45.2)		12.0 (0.5-23.0)		9.5 (2.6-35.0)	

* Mann-Whitney test

Median (range)

C group: GLM 50 mg/4 weeks + MTX group

M group: GLM 100 mg/4 weeks group

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MMP-3: matrix metalloproteinase-3, DAS: disease activity score, SDAI: simplified disease activity index, CDAI: clinical disease activity index, GLM: golimumab, MTX: methotrexate