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SHORT COMMUNICATION

Long-Term Maintenance of Golimumab Effectiveness for Injection Spacing in Rheumatoid Arthritis Patients with Low Disease Activity Who Previously Received Other TNF Inhibitors: Minimum 2-year Data From an Observational Study

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Abstract

Background Golimumab (GLM) has been reported to have lower immunogenicity than do other TNF inhibitors used for treating rheumatoid arthritis (RA). We previously found a prolonged effect of and improvement similar to that associated with infliximab (IFX) after switching to subcutaneous GLM (GLM-SC) for control of RA activity or adverse events. Thus, this study aimed to evaluate the continued maintenance of treatment efficacy and safety for > 2 years by switching to GLM-SC in RA patients with low disease activity or in remission after previous treatment with another tumor necrosis factor (TNF) inhibitor.

Methods Thirty-two patients treated with etanercept or infliximab were switched to GLM-SC and maintained low disease activity. The patients were divided into two groups (GLMq4w and GLMq8w) through discussion with each patient, considering their general condition and convenience. The groups included patients with low disease activity or in remission who switched to 50-mg GLM therapy at 4-week and 8-week intervals, respectively.

Results The mean DAS28-ESR and DAS-CRP values in the GLMq4w group (17 patients) and GLMq8w group (15 patients) were maintained from baseline throughout the 104-week treatment period. Two patients from the GLMq4w group showed disease flaring to moderate disease activity. No serious adverse events occurred, and the treatment continuation rate at 104 weeks was 100% in both groups. After > 2 years of treatment, three patients in the GLMq8w group and one patient in the GLMq4w group discontinued GLM treatment due to relapse or complications. The 5-year survival rates were 88.2% and 75.5% in the GLMq4w and GLMq8w groups, respectively. The average treatment duration was 5.0 (2.0–7.5) years.

Conclusion Administration of GLM-SC at 4-week and 8-week intervals after switching from TNF inhibitors showed sustained long-term efficacy and acceptable safety in RA patients with low disease activity.

Key Points

Administration of subcutaneous golimumab (GLM-SC) at 4- and 8-week intervals after switching from TNF inhibitors resulted in sustained efficacy and acceptable safety in rheumatoid arthritis patients with low disease activity.

Long-term GLM-SC treatment efficacy and safety were successfully maintained despite a long interval.

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1 Introduction

The treatment of rheumatoid arthritis (RA) is predominantly focused on controlling inflammation and pain, as well as slowing the progression of joint destruction and disability. The development of biologic disease-modifying anti-rheumatic drugs (DMARDs) represents a major breakthrough in the treatment of RA. These drugs could help achieve low disease activity (LDA) or even remission in patients with moderate-to-severe RA [1, 2].

Tumor necrosis factor (TNF)-α inhibitors tend to be the first agents prescribed when biologic DMARDs are indicated in RA, due to the wealth of evidence, experience, and long-term follow-up data. Although the efficacy of TNF-α inhibitors as treatments for patients with active RA has been widely demonstrated, some RA patients show decreased responsiveness after initially responding well to treatment. One of the potential reasons for the lack or loss of efficacy of the TNF inhibitors over time is the immunogenicity associated with biologic DMARDs. Thus, in such cases, it is useful to switch to a less immunogenic biologic agent to maintain disease activity and minimize adverse events [3].

Golimumab (GLM) is less immunogenic compared with the other TNF inhibitors used for RA treatment [4]. Our previous study indicated a prolonged effect and improvement similar to that associated with infliximab (IFX) after switching to subcutaneous GLM (GLM-SC) for control of disease activity or adverse events [5]. In patients with RA, the overall treatment satisfaction could be influenced by factors associated with the application of the biologic agent used, such as the route, timing, and frequency of administration. GLM-SC is convenient compared with intravenous infusion of TNF inhibitors and requires fewer injections compared with etanercept (ETN; 50 mg once weekly or 25 mg twice weekly). The purpose of this study was to evaluate continued maintenance of long-term treatment effectiveness and safety on switching to GLM-SC in RA patients with LDA or in remission who previously received another TNF inhibitor.

2 Patients and Methods

2.1 Patients and Golimumab Therapy Protocol

This was a simple observational study performed among 32 patients (25 female and 7 male patients) in whom treatment was switched to GLM-SC from other TNF inhibitors so as to ensure continuous LDA at Mie University and two other institutes.

The patients were divided into two dosing interval groups, as described previously [5]. At our center, the decision on the interval was made by the treating physician through a discussion with each patient, considering the patient's general condition and convenience. The GLMq4w group included 17 patients with LDA or in remission who switched to 50-mg GLM therapy at 4-week intervals and received methotrexate (MTX) concomitantly. The GLMq8w group included 15 patients with LDA or in remission who switched to 50-mg GLM therapy at 8-week intervals and received MTX concomitantly. In the GLMq4w group, 15 patients switched from IFX (200–300 mg/8 weeks) and two patients switched from ETN to GLM, while in the GLMq8w group, 14 patients switched from IFX and one patient switched from ETN. The ethics committee of Mie University approved this study (approval number: 2120).

2.2 Clinical Assessment

The follow-up assessment included observation of signs and symptoms and determination of the disease activity score (DAS) as described previously [5]. DAS28-erythrocyte sedimentation rate (ESR) [6] and DAS-C reactive protein (CRP) [7] were used to evaluate RA disease activity at 104 weeks and the latest follow-up compared with that at baseline. GLM continuation rates at 104 weeks and > 104 weeks (the latest follow-up) were also examined. For the safety evaluation, we assessed adverse events and serious adverse events leading to treatment discontinuation in each group. If patients discontinued GLM treatment before week 104, their data were analyzed by the last-observation-carried-forward method. The dose of concomitant MTX remained basically consistent; however, tapering of non-steroidal anti-inflammatory drugs and glucocorticoids was allowed during the study period.

2.3 Statistical Analysis

Differences between the groups in terms of swollen and tender joint counts, patient global assessment, ESR, CRP, and DAS28-ESR and DAS-CRP scores were determined using the Wilcoxon rank-sum test, analysis of variance, Pearson's test, or the Tukey–Kramer honestly significant difference test. Survival distribution curves were computed by the Kaplan–Meier method. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 26 (IBM Japan, Tokyo, Japan).

3 Results

3.1 Patients' Characteristics

The patients' mean age was 63.9 years (range 42–80) at the start of GLM treatment. Table 1 shows the baseline

Table 1 Patients' characteristics

	GLMq4w group ($n = 17$)	GLMq8w group ($n = 15$)	p value
Female n (%)	15 (88.2)	10 (66.7)	0.210
Age, years	67 [55–72]	64 [58 72]	0.781
RA disease duration, years	10.6 [9–22.8]	6.1 [2.8–10.6]	0.010*
Steinbrocker stage (I/II/III/IV)	0/7/6/4	0/7/7/1	0.396
Steinbrocker class (1/2/3/4)	2/12/2/1	1/12/2/0	0.811
Body weight (kg)	53.0 [38–63]	54.2 [47–61.6]	0.207
BMI	21.9 [20.1–23.5]	22.5 [20.3–24.7]	0.548
Tender joint count	0 [0–1]	0 [0–1]	0.798
Swollen joint count	0 [0–0]	0 [0–0]	0.917
Patient's global assessment score (mm)	15 [3–25]	7 [0–16]	0.273
ESR (mm/h)	12 [7–17]	7 [5–14]	0.153
CRP (mg/dL)	0.06 [0.025–0.18]	0.22 [0.05–0.23]	0.411
RF	65 [27.5–108]	61 [5.5–267.5]	0.710
MMP3 (ng/mL)	34.7 [27.8–64.7]	71.0 [47–108.5]	0.183
DAS28-ESR	2.23 [1.50–2.55]	1.95 [1.16–2.55]	0.147
DAS28-CRP	1.46 [1.27–2.26]	1.60 [1.11–2.15]	0.783
Methotrexate use, n (%)	16 (94.1)	15 (100)	0.356
Methotrexate dose (mg/week)	6 [5–7]	6 [4–8]	0.875
Corticosteroid use, n (%)	6 (35.2)	12 (80.0)	0.032*
Corticosteroid dose (mg/day)	2.5 [0–2.5]	5 [2–5]	0.035*
Treatment duration of TNF inhibitor (years)	6.1 [3.9–7.5]	4 [1.3–7.4]	0.546
Prior anti-TNF agent (infliximab/etanercept)	15/2	14/1	0.999

The RA disease duration was shorter in the GLMq8w group, and this group had a higher number of patients using corticosteroids than did the GLMq4w group. However, intergroup differences in serum markers or disease activity at baseline were not significant

Results are expressed as median [interquartile range] values unless otherwise stated

BMI body mass index, *CRP* C-reactive protein, *DAS28* disease activity score 28, *ESR* erythrocyte sedimentation rate, *GLM* golimumab, *MMP3* matrix metalloproteinase-3, *PaGA* Patient's Global Assessment score, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *TNF* tumor necrosis factor

characteristics of the patients. The percentage of patients who received corticosteroids in the GLMq4w group was significantly lower than that in the GLMq8w group ($p < 0.05$) (Table 1). In the GLMq8w group, RA duration was significantly shorter than that in the GLMq4w group ($p = 0.01$). However, intergroup differences in serum markers or disease activity at baseline were not significant.

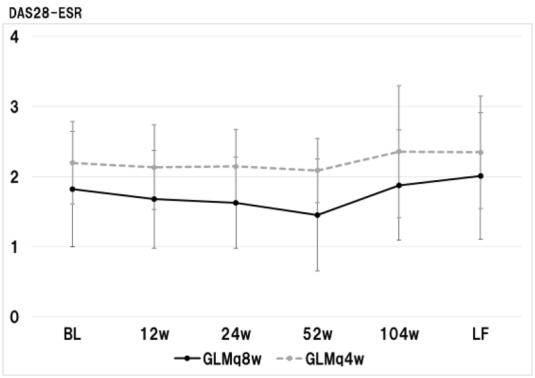
3.2 Efficacy, Adverse Events, and Survival Analyses

The mean DAS28-ESR and DAS28-CRP values in the GLMq4w and GLMq8w groups were maintained from baseline throughout the 104-week treatment period (Fig. 1a,b). In the GLMq4w and GLMq8w groups, respectively, DAS28-ESR remission (< 2.6) rates (58.8% and 73.3%) and LDA (< 3.2) rates (88.2% and 100%), and DAS28-CRP remission (< 2.3) rates (88.2% and 86.7%) and LDA (< 2.7) rates (88.2% and 100%) were also maintained at week 104 (Fig. 1c,d). The disease activity increased to a moderate level in two patients in the GLMq4w group. One patient was transferred to another hospital while continuing GLM treatment, and the GLM dose was increased to 100 mg once every 4 weeks for the other patient.

Adverse events through week 104 of this study are shown in Table 2. Infections were the most reported adverse events across both treatment groups, occurring in 23.5% and 20% of patients in the GLMq4w and GLMq8w groups, respectively. The incidence of infections was, thus, the same in both groups. No serious adverse event or injection-site reaction occurred, and the treatment continuation rate at 104 weeks was 100% in both groups.

After > 2 years (104 weeks) of treatment, the DAS28-ESR LDA rates (88.2% and 93.3%) and DAS28-CRP LDA rates (88.2% and 86.7%) were also maintained at the latest follow-up in the GLMq4w and GLMq8w groups, respectively (Fig. 1c, d). However, one patient in the GLMq8w group discontinued GLM treatment due to relapse to moderate disease. Furthermore, one patient (uterine cancer) in the GLMq4w group and two patients (MTX-related lymphoproliferative disorder and postoperative infection in the spine) in the GLMq8w group discontinued GLM treatment due to complications. The 5-year survival rates associated with

A



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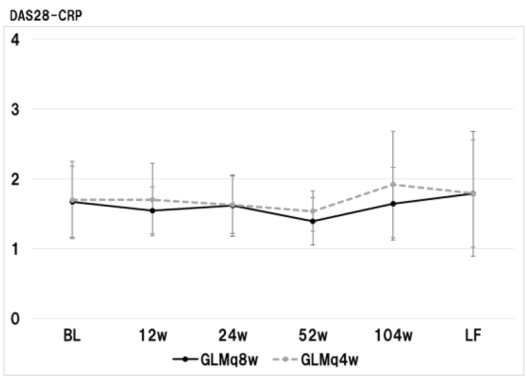

	BL	12w	24w	52w	104w	LF
GLM q4w	2.19 ±0.59	2.13 ±0.60	2.14 ±0.52	2.09 ±0.46	2.36 ±0.94	2.34 ±0.81
GLM q8w	1.82 ±0.82	1.68 ±0.70	1.62 ±0.65	1.45 ±0.80	1.88 ±0.79	2.01 ±0.91

	BL	12w	24w	52w	104w	LF
GLM q4w	1.70 ±0.55	1.70 ±0.52	1.63 ±0.41	1.54 ±0.29	1.92 ±0.76	1.79 ±0.77
GLM q8w	1.67 ±0.51	1.54 ±0.34	1.61 ±0.44	1.39 ±0.38	1.64 ±0.52	1.79 ±0.89

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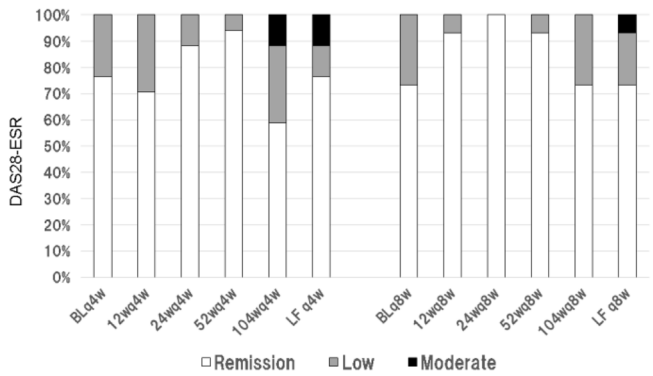

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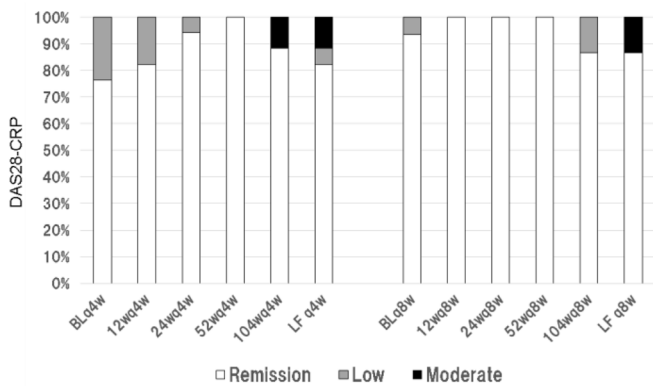

◂**Fig. 1** Changes in measured disease activity (**a** DAS28-ESR; **b** DAS28-CRP), rates of remission, and low and moderate disease activity (**c** DAS28-ESR; **d** DAS28-CRP) before treatment and at weeks 12, 24, 52, and 104, and at the latest follow-up in each group. Overall disease control was maintained after switching from infliximab or etanercept to subcutaneous golimumab in both groups. *LF* latest follow up, *DAS28* disease activity score 28, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

GLM continuation in the GLMq4w and GLMq8w groups were 88.2% and 75.5%, respectively (Fig. 2). The average treatment duration was 5.0 (2.0–7.5) years.

4 Discussion

Biologic medications such as subcutaneous TNF-α inhibitors (SC-TNFis) have transformed the management of diseases [8]. Furthermore, the administration of biologic medications with higher persistence rates is beneficial for maintaining disease activity in patients. The availability of biologic agents specifically for RA has expanded treatment options in terms of route and timing of administration as well as the range of possible toxicities and cost of therapy [9]. Treatments with biologics may or may not include an induction period and the administration could range from twice a week to once every 8 weeks. These factors can influence patients' overall satisfaction with their treatment, because the mode and frequency of treatment administration are important to patients with RA.

GLM-SC was associated with a better treatment effect and survival rate than were other TNF inhibitors [10–12]. These reports support the notion that GLM may have better real-world persistence of the treatment effect. In vitro bioassays showed that the affinity of GLM for soluble TNFα and its ability to neutralize it were similar to those of ETN and greater than those of IFX and adalimumab (ADA). These results suggest that a lower serum concentration of GLM, compared with that of IFX or ADA, would have similar pharmacological effects in patients [13].

In our previous study, among patients with RA whose treatment was switched from IFX or ETN to GLM-SC 50 mg every 4 or 8 weeks, clinical improvement continued from week 0 to week 52 of the study [14]. Here, we report the results from the second year of treatment. Both GLM-SC treatment regimens with 4- and 8-week intervals secondary to TNF inhibitors were effective in maintaining the clinical response achieved with LDA. Furthermore, the continuation rate of GLM treatment at 2 years was 100% in both groups. The 5-year survival rates associated with the continuation of GLM treatment were 88.2% and 75.5% in the GLMq4w and GLMq8w groups, respectively.

GLM has been developed with an innovative technology that minimizes immunogenicity [4, 15]. In recent studies, the 2-year survival associated with GLM treatment was 51.9–73.1% among those whose response to biologics was inadequate and in biologic-naive patients [16, 17]. Gomides et al. reported that GLM was associated with fewer episodes of discontinuation due to secondary inefficiency [18]. This result may be due to the low immunogenicity of GLM. The prescribing information for GLM-IV specifies a dosing regimen of 2 mg/kg at maintenance therapy every 8 weeks thereafter. GLM can be administered by subcutaneous injection as well as by intravenous infusion. GLM-SC is the only biologic agent approved for the treatment of RA in Japan. In our study, one of the reasons for the continued maintenance of disease activity even with an 8-week interval between consecutive GLM doses may be that this dose interval results in less immunogenicity. For other reasons, in the GO-SAVE trial, most patients with RA who transitioned to GLM from ADA or ETN were satisfied with their overall GLM experience. Patients who received GLM-SC through week 44 reported much less discomfort, redness, pain, stinging, and burning with the GLM injection than with their previous injections with TNF inhibitors [19]. Bolge et al. reported that injection experience is an often-cited reason for the discontinuation of anti-TNF medication by patients with RA [20]. The less severe injection-site reaction and the longer administration interval may have contributed to the treatment continuation rate.

Our data suggest that a shorter disease duration enables successful maintenance of GLM treatment despite a long interval between doses. In previous reports, the predictors of GLM discontinuation in patients were female sex, GLM monotherapy [16, 17], and failing to early achievement of a good European League Against Rheumatism (EULAR) response in RA [17]. Another reason for the good treatment continuation rate in the GLMq8w group in this study could be that the MTX use rate was 100% and that there were many male patients. In addition, the reason the continuation rate was good in both groups was the possibility of switching in case of LDA, which seems to be effective in maintaining disease activity.

The key limitations of this study are the smaller number of patients who received open-label GLM-SC. Furthermore, radiographic data were lacking, leading to the possibility that some patients may have had residual disease activity and consequent structural damage. We think that such effects were at best small, if they existed, because of LDA maintenance.

5 Conclusion

Long-term administration of GLM-SC was associated with continuing efficacy in patients with RA. GLM-SC was well tolerated and LDA was maintained in both the GLMq4w and GLMq8w groups, with no new safety concerns identified.

Table 2 Adverse events through 2 years of GLM treatment

Through week 104	GLMq4w group ($n = 17$)	GLMq8w group ($n = 15$)
Common cold	1	3
Upper respiratory tract infection	2	
Conjunctivitis	1	
Vertigo		1
Esophageal ulcer		1
Interstitial lung disease	1 (reduced MTX)	
Liver function test abnormalities	1 (reduced MTX)	
Laboratory abnormality	5	8
Adverse events occurring after the 2-year study period (year of GLM treatment)	GLMq4w group	GLMq8w group
Uterine cancer	1 (2.25 years)	
Postoperative infection in the spine		1 (4.25 years)
MTX-related lymphoproliferative disorders		1 (4.33 years)
Secondary loss of efficacy		1 (3.5 years)

Adverse events requiring a reduction in the methotrexate dose included worsening of interstitial lung disease and liver function in one patient each in the GLMq4w group

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

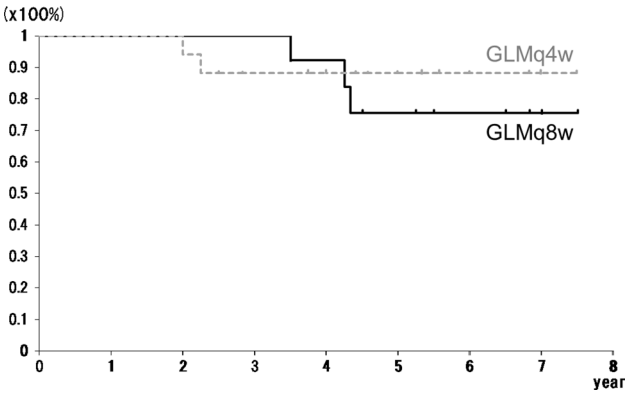

Fig. 2 Survival rates associated with the continuation of golimumab treatment

Declarations

Funding No benefits or funds were received in support of the study.

Conflict of Interest The authors declare that they have no conflict of interests.

Ethics approval The ethics committee of Mie University approved this study (approval number: 2120).

Consent to participate All participants gave their written agreement to participate in the study.

Availability of data and material Not applicable.

Code availability Not applicable.

Author Contributions HW was involved in the study design, acquisition and analysis of data, and interpretation of the results. NN, HI, and YN were involved in the acquisition and analysis of data. MH and AS were involved in the design of the study and interpretation of the results. All authors contributed toward critical revisions of the manuscript for important intellectual content and approved the final version of the article to be submitted.

References

1. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685–99.
2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580–8.

3. Mok CC, Tsai WC, Chen DY, Wei JC. Immunogenicity of anti-TNF biologic agents in the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2016;16:201–11.
4. Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis. 2013;72:165–78.
5. Wakabayashi H, Inada H, Nishioka Y, Hasegawa M, Nishioka K, Sudo A. Efficacy of switching from infliximab to subcutaneous golimumab in patients with rheumatoid arthritis to control disease activity or adverse events. Drugs R D. 2017;17:233–9.
6. DAS-SCORE.NL. The Netherlands; 2020. http://www.das-score.nl/.
7. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis. 2007;66:407–9.
8. Blum MA, Koo D, Doshi JA. Measurement and rates of persistence with and adherence to biologics for rheumatoid arthritis: a systematic review. Clin Ther. 2011;33:901–13.
9. Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. Patient Prefer Adherence. 2009;3:335–44.
10. Khalil H, Tahami A. Golimumab drug utilization patterns in Canada—higher retention rate in golimumab treated rheumatoid patients arthritis patients compared to etanercept and adalimumab [Abstract]. Arthritis Rheum. 2012;64(Suppl 10):497.
11. Favalli EG, Sinigaglia L, Becciolini A, et al. Two-year persistence of golimumab as second-line biologic agent in rheumatoid arthritis as compared to other subcutaneous tumor necrosis factor inhibitors: real-life data from the LORHEN registry. Int J Rheum Dis. 2018;21:422–30.
12. Dalén J, Svedbom A, Black CM, et al. Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence. Rheumatol Int. 2016;36:987–95.
13. Shealy DJ, Cai A, Staquet K, Baker A, Lacy ER, Johns L, Vafa O, Gunn G 3rd, Tam S, Sague S, Wang D, Brigham-Burke M, Dalmonte P, Emmell E, Pikounis B, Bugelski PJ, Zhou H, Scallon BJ, Giles-Komar J. Characterization of golimumab, a human monoclonal antibody specific for human tumor necrosis factor α. MAbs. 2010;2(4):428–39.
14. Wakabayashi H, Inada H, Nishioka Y, Hasegawa M, Sudo A, Nishioka K. Maintenance of efficacy and safety with subcutaneous golimumab in rheumatoid arthritis patients with low disease activity who previously received TNF inhibitors. Clin Rheumatol. 2017;36:941–6.
15. Weinblatt ME, Bingham CO 3rd, Mendelsohn AM, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis. 2013;72:381–9.
16. Iannone F, Favalli EG, Caporali R, et al. Golimumab effectiveness in biologic inadequate responding patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis in real-life from the Italian registry GISEA. Jt Bone Spine. 2021;88(1):105062.
17. Iannone F, Santo L, Anelli MG, et al. Golimumab in real-life settings: 2 Years drug survival and predictors of clinical outcomes in rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. Semin Arthritis Rheum. 2017;47:108–14.
18. Gomides APM, de Albuquerque CP, Santos ABV, et al. Real-life data of survival and reasons for discontinuation of biological disease-modifying drugs 'in' rheumatoid arthritis. Int J Clin Pharm. 2020. https://doi.org/10.1007/s11096-020-01171-5.
19. Dehoratius RJ, Brent LH, Curtis JR, Ellis LA, Tang KL. Satisfaction with subcutaneous golimumab and its auto-injector among rheumatoid arthritis patients with inadequate response to adalimumab or etanercept. Patient. 2018;11:361–9.
20. Bolge SC, Goren A, Tandon N. Reasons for discontinuation of subcutaneous biologic therapy in the treatment of rheumatoid arthritis: a patient perspective. Patient Prefer Adherence. 2015;9:121–31.