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Effectiveness and Factors Associated with Response to Golimumab in Japanese Patients with Ulcerative Colitis in Real Clinical Practice: The Phoenix Study

Daisuke Hirayama[a] Satoshi Motoya[b] Toshifumi Ashida[c] Katsuyoshi Ando[d] Mikihiro Fujiya[d] Takahiro Ito[e] Shigeru Furukawa[e] Atsuo Maemoto[e] Takehiko Katsurada[f] Shiro Hinotsu[g] Noriko Sato[h] Naomi Mizuno[h] Yoshiko Ikawa[h] Hiroshi Nakase[a]

[a]Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, Sapporo, Japan; [b]IBD Center, Sapporo Kosei General Hospital, Sapporo, Japan; [c]Inflammatory Bowel Disease Center, Sapporo Tokushukai Hospital, Sapporo, Japan; [d]Gastroenterology and Endoscopy, Division of Metabolism and Biosystemic Science, Gastroenterology, and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan; [e]Inflammatory Bowel Disease Center, Sapporo Higashi Tokushukai Hospital, Sapporo, Japan; [f]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University, Sapporo, Japan; [g]Department of Biostatistics and Data Management, Sapporo Medical University of Medicine, Sapporo, Japan; [h]Ikuyaku, Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

Keywords
Golimumab · Ulcerative colitis · Real-world effectiveness · Anti-TNF-α antibody

Abstract
Introduction: There have been limited reports on the clinical efficacy of golimumab (GLM) in Japanese patients with ulcerative colitis (UC) in real clinical practice. This study aimed to explore the real-life effectiveness and factors associated with response to GLM in Japanese patients with UC. ***Methods:*** This observational, retrospective, multicenter study was conducted in hospitals with expertise in inflammatory bowel disease treatment. Sixty-three patients treated with GLM and active UC were included in the analysis. Clinical remission (CR) (partial Mayo (pMayo) score ≤2) in the induction and maintenance phases after GLM treatment and associated factors were evaluated. ***Results:*** The proportion of patients achieving CR in the induction and maintenance phases was 41.3% (26/63) and 46.0% (29/63, the last observation carried forward method was used for patients who discontinued treatment for reasons other than inadequate response), respectively. The median pMayo score was 5 (interquartile range (IQR): 4–6) at baseline, 3 (IQR: 1–5) in the induction phase, and 1 (IQR: 0–3) in the maintenance phase. Hemoglobin, platelet, and C-reactive protein levels changed, consistent with the pMayo score. Multivariate logistic analysis revealed that biologic-naive status was an independent factor associated with CR in the induction ($p = 0.0200$) and maintenance ($p = 0.0459$) phases, and a disease duration of >60 months until GLM initiation was associated with CR in the induction phase

karger@karger.com
www.karger.com/iid

Correspondence to:
Hiroshi Nakase, hiropynakase@gmail.com

($p = 0.0427$). ***Conclusions:*** The effectiveness of GLM in daily clinical practice has been confirmed in Japanese patients with active UC. Biologic-naive patients responded more to GLM in the induction and maintenance phases, and patients with disease duration of >60 months until initiation of GLM were more responsive in the induction phase.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) limited to the colon and characterized by relapsing and remitting mucosal inflammation. Based on population-based cohort studies [1], the majority of patients with UC have a mild-to-moderate course, generally most active at diagnosis and varying periods of remission or mild activity. Approximately 15% of patients experience an aggressive course and almost 50% of patients require UC-related hospitalization at some point during the disease course [1]. Therefore, to improve the quality of life of patients with UC, treatments should aim for rapid and long-term induction of remission. However, the pathogenesis of UC is complex due to the involvement of various cytokines. Therefore, UC treatment should be decided based on patient background, clinical symptoms, biomarkers, and endoscopic findings. The recent advent of biological agents has significantly revolutionized UC treatment. Currently, five biological agents, infliximab (IFX), adalimumab (ADA), golimumab (GLM), vedolizumab (VDZ), and ustekinumab (UST), are available for the treatment of UC. These drugs have various levels of efficacy and are recommended as first-line treatment for moderate-to-severe UC. However, the selection criteria for these drugs are not precise. GLM is a subcutaneously administered fully human anti-tumor necrosis factor-α (TNF-α) antibody. Several clinical trials [2, 3] and real-world data [4–21] outside Japan have demonstrated the clinical efficacy and safety of GLM in induction and maintenance therapy in patients with moderate-to-severe active UC. In addition, the PURSUIT-J study showed that GLM treatment for 54 weeks maintained clinical efficacy and safety through week 54 among induction responders in biologic-naïve Japanese patients with moderate-to-severe active UC [22]. However, there have been limited reports on the effectiveness and safety of GLM in Japanese UC patients in real clinical practice [23]. In addition, the characteristics of patients who respond to GLM treatment, including the impact of prior therapy and concomitant medications, are not fully understood. In this study, we investigated the treatment effectiveness of GLM and factors related to GLM response using cohort data from the Principal Research in the Hokkaido Organization Emphasizing Nutritional and Therapeutic Improvement to IBD Patients' Expectation (Phoenix) study.

Materials and Methods

Study Design and Population

This was an observational, retrospective, multicenter study conducted in Hokkaido, Japan. UC patients who commenced GLM treatment at six hospitals from April 2017 to March 2021 were included. UC was diagnosed based on the criteria determined by the Japanese Ministry of Health, Labor, and Welfare [24]. Patients received GLM per the approved label in Japan (200 mg at week 0 and 100 mg at week 2, followed by 100 mg every 4 weeks). The exclusion criteria were patients with a history of extensive colonic resection, a partial Mayo (pMayo) score of ≤ two points or unknown at the initiation of GLM, or patients who discontinued GLM treatment for 6 weeks. Patients who discontinued GLM by 6 weeks because they achieved clinical remission (CR) were also excluded. The Phoenix study group determined the research protocol for this analysis. This study was approved by the University Hospital Medical Information Network Center (UMIN 000035384; available at http://www.umin.ac.jp/ctr/).

Data Collection

The baseline characteristics collected from the medical records included age, sex, body mass index (BMI), disease duration, disease location according to the Montreal Classification system, extra-intestinal manifestations, response to corticosteroids (CSs), concomitant UC therapies (including 5-aminosalicylic acid (5-ASA), CSs, immunomodulators, IFX, ADA, VDZ, UST, cytapheresis, and budesonide foam), Mayo score, pMayo score, C-reactive protein (CRP, mg/dL) level, hemoglobin (Hb, g/dL) level, platelet level ($\times 10^4/\mu L$), Mayo endoscopic subscore (MES), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Matts classification. Follow-up data were collected during the induction phase defined as 6–14 weeks, the maintenance phase defined as 44–60 weeks, and at the last follow-up visit. Safety outcomes (death, serious infection, colon cancer/dysplasia, cancer other than colorectal cancer) and history of total colectomy after initiation of GLM treatment were also collected.

Outcomes and Definitions

The Mayo score was determined at the baseline, induction, and maintenance phases after initiation of GLM treatment. Additionally, mucosal inflammation was assessed during each colonoscopy according to the MES and UCEIS scores at baseline and 52 weeks after the commencement of GLM. CR was defined as a pMayo score of ≤ two points or fewer. Clinical response was defined as a decrease in the pMayo score by two points or 30% after treatment. We judged that patients who discontinued GLM owing to an inadequate response before 44 weeks did not achieve CR or clinical response in the maintenance phase. For patients who discontinued GLM for other reasons, we used the last observation carried forward (LOCF) method to impute the data from the pMayo score.

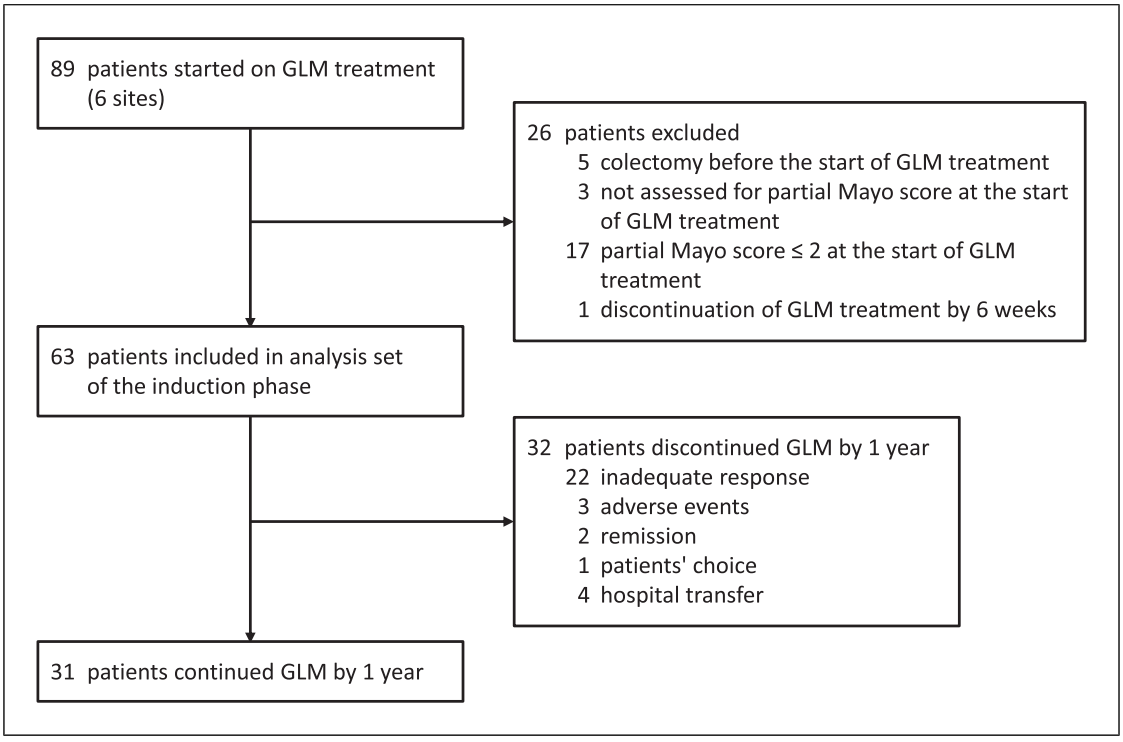

Fig. 1. Study flow chart and numbers of patients. GLM, golimumab.

The endpoints of this study were the proportion of patients achieving CR and clinical response in the induction and maintenance phases after GLM treatment, change in pMayo score and biomarker levels (Hb, platelets, and CRP) during GLM treatment, factors at GLM treatment initiation associated with CR in the induction and maintenance phases after GLM treatment, and persistency ratio of GLM treatment.

Statistical Methods

Continuous and ordinal variables were presented as medians with interquartile range (IQR). The associated variables were assessed using univariate and multivariate logistic regression analysis. Covariates in multivariate analyses were selected based on the results of univariate analyses ($p < 0.2$) and their possible associations with the outcomes. Results were expressed as odds ratios (ORs) and 95% confidence intervals. Significant differences between outcomes were indicated as p values <0.05. The Kaplan-Meier method was used to assess the persistence of GLM. All statistical analyses were performed using JMP 15, JMP Pro, Version 15 software, Microsoft® Windows® for × 64; SAS Institute Inc., Cary, NC, USA, 1989–2019.

Results

Baseline Characteristics

A total of 89 patients commenced GLM treatment in this retrospective cohort study, and 63 patients with active UC were included in the analysis set of the induction phase (Fig. 1). Among them, 31 continued GLM treatment for 1 year. The baseline characteristics and concomitant use during GLM treatment of the included patients are shown in Table 1. The median age at the initiation of GLM treatment was 44 years. Twenty-four patients (38.1%) were male. The median disease duration was 57 months. Most of the patients had extensive colitis (85.7%). The CS-dependent and CS-resistant cases accounted for 61.0% and 30.5%, respectively. Thirty-six patients were exposed to more than one biological agent. Among them, 33 patients were exposed to anti-TNF-α antibodies other than GLM. Immediately before GLM treatment, 46.8% received CSs, 39.7% received biologics, and 12.9% underwent cytapheresis. The median Mayo score, MES, and UCEIS score were 7, 2, and 5, respectively. The median CRP level was 0.30 mg/dL.

Proportion of CR and Response Induced by GLM

Thirty-two patients discontinued GML in the maintenance phase (Fig. 1). Twenty-two patients who could not continue GLM owing to inadequate response were not considered to have CR or clinical response. For 10 patients who could not continue GLM for other reasons, we imputed the data using the LOCF method. The

Table 1. Baseline characteristics and concomitant medication

Sex, male	*N* = 63	24 (38.1%)
Age at diagnosis of UC, years	*N* = 63	35 (24–46)
Age at the start of GLM treatment, years	*N* = 63	44 (32–57)
Duration of disease until initiation of GLM treatment, months	*N* = 63	57 (28–96)
BMI	*N* = 57	22.9 (19.0–26.3)
Extent of disease		
Proctitis	*N* = 63	1 (1.6%)
Left-side	*N* = 63	8 (12.7%)
Pancolitis	*N* = 63	54 (85.7%)
Extra-intestinal manifestations		
None	*N* = 63	55 (87.3%)
Arthropathy	*N* = 63	4 (6.3%)
Cutaneous	*N* = 63	1 (1.6%)
Ocular	*N* = 63	0 (0.0%)
Hepatobiliary and pancreatic disease	*N* = 63	2 (3.2%)
Thrombosis	*N* = 63	0 (0.0%)
Others	*N* = 63	1 (1.6%)
Response to CS		
CS-responder	*N* = 59	5 (8.5%)
CS-dependent	*N* = 59	36 (61.0%)
CS-resistant	*N* = 59	18 (30.5%)
Prior use of 5-aminosalicylic acid	*N* = 63	63 (100%)
Prior use of CS	*N* = 63	59 (93.7%)
Cumulative dose of CS until initiation of GLM treatment, mg	*N* = 40	2,944 (1,634–4,034)
Duration of CS use until initiation of GLM treatment, day	*N* = 52	186 (103–365)
Prior use of immunomodulators	*N* = 63	49 (77.8%)
Prior use of biologics	*N* = 63	36 (57.1%)
1 biologic	*N* = 36	22 (61.1%)
2 biologics	*N* = 36	11 (30.6%)
3 biologics	*N* = 36	2 (5.6%)
4 biologics	*N* = 36	1 (2.8%)
1 anti-TNF-α antibody	*N* = 36	22 (61.1%)
2 anti-TNF-α antibody	*N* = 36	10 (27.8%)
3 anti-TNF-α antibody	*N* = 36	1 (2.8%)
Infliximab	*N* = 63	25 (39.7%)
Infliximab-biosimilar	*N* = 63	2 (3.2%)
Adalimumab	*N* = 63	18 (28.6%)
Vedolizumab	*N* = 63	9 (14.3%)
Ustekinumab	*N* = 63	0 (0.0%)
Prior use of budesonide foam	*N* = 63	23 (36.5%)
Therapy used immediately before GLM treatment		
CS	*N* = 62	29 (46.8%)
Biologics	*N* = 63	25 (39.7%)
Cytapheresis	*N* = 62	8 (12.9%)
Disease activity at initiation of GLM treatment		
Mayo score	*N* = 42	7 (6–8)
pMayo score	*N* = 63	5 (4–6)
MES	*N* = 42	2 (2–3)
UCEIS	*N* = 37	5 (4–6)
Matts classification	*N* = 30	5 (3–5)
Hb, g/dL	*N* = 62	11.3 (10.0–12.5)
Platelet, $\times 10^4/\mu L$	*N* = 62	31.3 (25.3–37.7)
CRP, mg/dL	*N* = 62	0.30 (0.05–1.04)
Concomitant medication		
5-Aminosalicylic acid	*N* = 62	40 (64.5%)
CS	*N* = 62	24 (38.7%)

Table 1 (continued)

Immunomodulator at initiation of GLM treatment	*N* = 62	32 (51.6%)
Immunomodulator in the induction phase	*N* = 62	32 (51.6%)
Immunomodulator in the maintenance phase	*N* = 33	15 (45.5%)

Data are *N* (%) or median (IQR). BMI, body mass index; CRP, C-reactive protein; GLM, golimumab; IQR, interquartile range; MES, Mayo endoscopic subscore; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

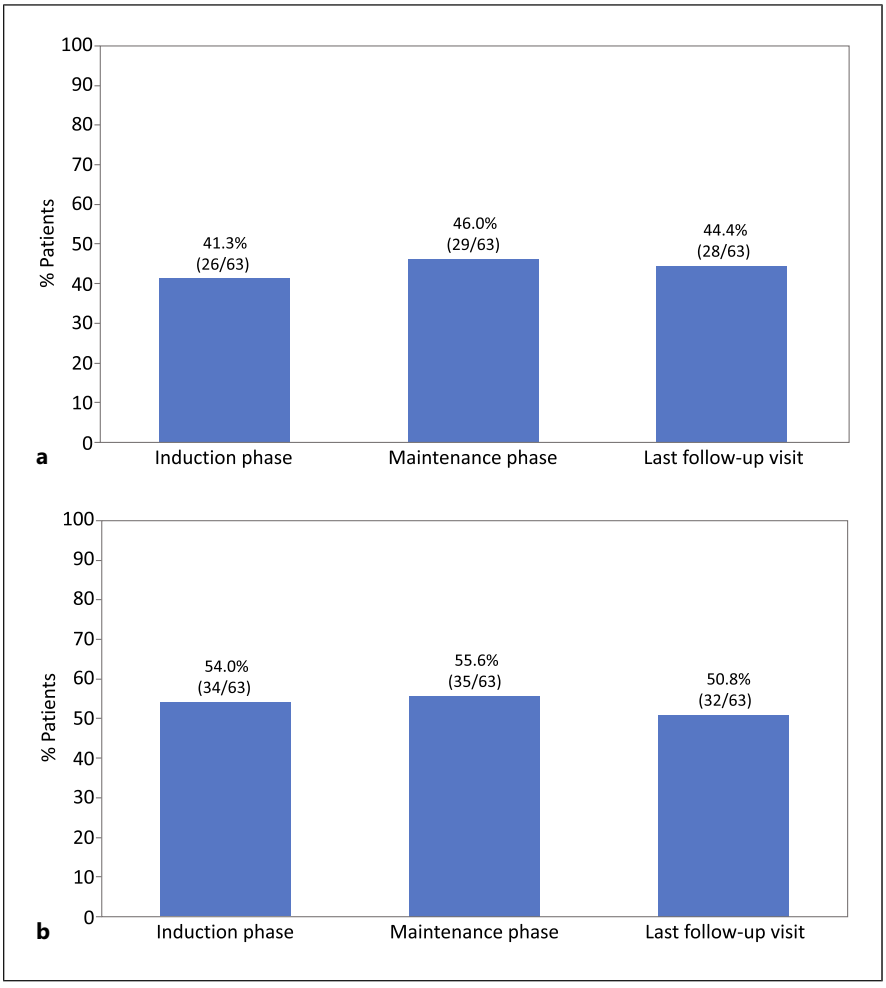

Fig. 2. a Proportions of patients achieving CR in the induction phase (6–14 weeks), maintenance phase (44–60 weeks), and last follow-up visit after commencing GLM treatment. **b** Proportions of patients achieving clinical response in the induction phase (6–14 weeks), maintenance phase (44–60 weeks), and last follow-up visit after starting GLM treatment. Twenty-two patients who could not continue GLM owing to inadequate response were not considered to have CR or clinical response. For 10 patients who could not continue GLM for other reasons, we imputed the data using the LOCF method. GLM, golimumab; LOCF, last observation carried forward; CR, clinical remission.

proportion of patients achieving CR in the induction phase, maintenance phase, and last follow-up visit (median treatment duration: 335 days) were 41.3% (26/63), 46.0% (29/63), and 44.4% (28/63), respectively (Fig. 2a). The proportions of patients achieving clinical response in the induction phase, maintenance phase, and last follow-up visit were 54.0% (34/63), 55.6% (35/63), and 50.8% (32/63), respectively (Fig. 2b).

Changes in pMayo Score and Biomarkers

The median pMayo score was 5 (IQR: 4–6, *n* = 63) at baseline, 3 (IQR: 1–5, *n* = 63) in the induction phase, and 1 (IQR: 0–3, *n* = 31) in the maintenance phase (Fig. 3a). Consistent with the pMayo score data, there were also changes in Hb, platelet, and CRP levels between the baseline and maintenance phases (Fig. 3b–d).

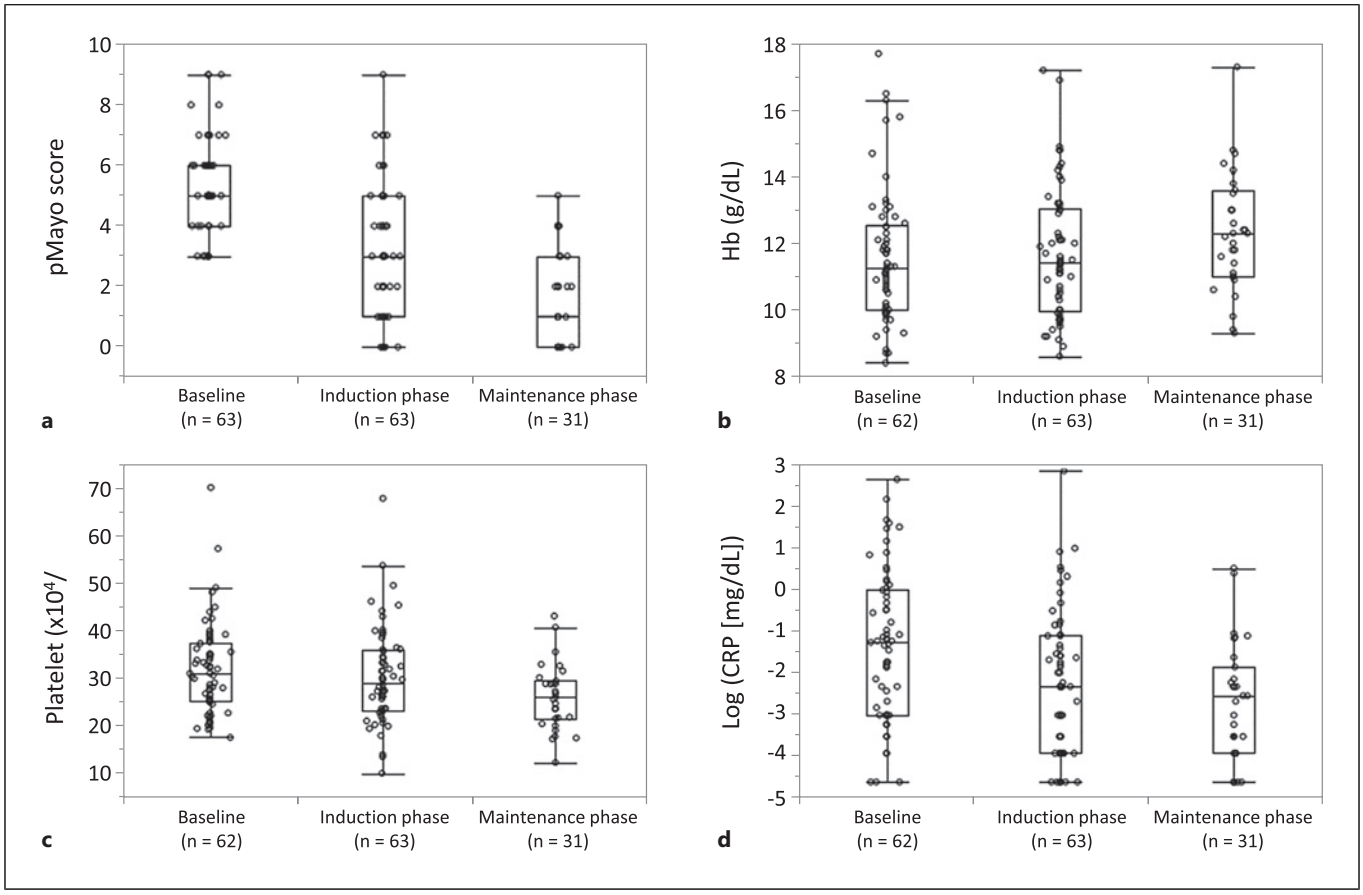

Fig. 3. Changes in pMayo score (**a**), Hb levels (**b**), platelet levels (**c**), and CRP levels (**d**) from baseline to induction phase (6–14 weeks) and maintenance phase (44–60 weeks). Box and whisker plots showing median values, upper and lower quartiles, and 1.5 times quartile range. CRP, C-reactive protein; Hb, hemoglobin; pMayo, partial Mayo.

Identification of Factors Associated with Achievement of CR

During the induction phase of GLM treatment, univariate analysis revealed that age >35 years at the diagnosis of UC (OR: 2.954, $p = 0.0384$), age >45 years at the initiation of GLM treatment (OR: 2.954, $p = 0.0384$), and no prior use of biologics (OR: 2.841, $p = 0.0461$) were significantly associated with CR (Table 2). Notably, no significant difference in the proportion of patients achieving CR in the induction phase was observed between patients with a history of one biological treatment and those who received two or more biologics (OR: 1.167, $p = 0.8367$) (Table 2). In addition, whether patients achieved CR by other biological therapies immediately before GLM treatment was significantly associated with a higher proportion of CR after induction of treatment with GLM (CR, 50.0% [5/10] versus not (CR, 10.5% [2/19], OR: 8.500 [95% confidence interval: 1.247–57.931], $p = 0.0182$), even though the sample size was limited. In the multivariate analysis using age at UC diagnosis, disease duration until initiation of GLM treatment, prior biological use (IFX, IFX biosimilar [IFX-BS], ADA, VDZ, and UST), no prior biological use (OR: 4.221, $p = 0.0200$), and disease duration of >60 months until initiation of GLM treatment (OR: 3.484, $p = 0.0427$) were independent factors associated with CR (Table 3). Age >35 years at diagnosis also tended to be associated with CR (OR: 2.795, $p = 0.0717$). Since sex and BMI have been reported to be associated with trough concentrations of biologics [25–27], a multivariate analysis with sex and BMI as covariates was also performed. As a result, no prior biologic use (OR: 3.636, $p = 0.0355$) remained significant, and age >35 years at diagnosis tended to be significant (OR: 3.203, $p = 0.0511$), whereas disease duration greater than 60 months until the initiation of

Table 2. Factors related to CR after golimumab treatment, using univariate logistic regression analysis

	In the induction phase (at 6–14 weeks)			In the maintenance phase (at 44–60 weeks)		
	CR, *n* (%)	OR 95% CI	*p* value*	CR, *n* (%)	OR 95% CI	*p* value*
Sex						
Male	9/24 (37.5)	0.776 (0.274, 2.199)	0.6335	10/24 (41.7)	0.752 (0.269, 2.098)	0.5855
Female	17/39 (43.6)	1		19/39 (48.7)	1	
Age at diagnosis of UC						
>35 years	16/29 (55.2)	2.954 (1.045, 8.350)	0.0384	16/29 (55.2)	1.988 (0.726, 5.442)	0.1788
≤35 years	10/34 (29.4)	1		13/34 (38.2)	1	
Age at initiation of GLM treatment						
>45 years	16/29 (55.2)	2.954 (1.045, 8.350)	0.0384	15/29 (51.7)	1.531 (0.564, 4.154)	0.4025
≤45 years	10/34 (29.4)	1		14/34 (41.2)	1	
Duration of disease until initiation of GLM treatment						
>60 months	15/28 (53.6)	2.517 (0.899, 7.052)	0.0761	15/28 (53.6)	1.731 (0.634, 4.726)	0.2829
≤60 months	11/35 (31.4)	1		14/35 (40.0)	1	
BMI						
≤22	8/25 (32.0)	0.605 (0.203, 1.804)	0.3660	9/25 (36.0)	0.638 (0.218, 1.862)	0.4093
>22	14/32 (43.8)	1		15/32 (46.9)	1	
Extent of disease						
Extensive	21/53 (39.6)	1	0.5410	23/53 (43.4)	1	0.3339
Others	5/10 (50.0)	1.524 (0.393, 5.915)		6/10 (60.0)	1.957 (0.494, 7.752)	
Response to CS						
CS-responder	2/5 (40.0)		0.2928	2/5 (40.4)		0.8291
CS-dependent	12/36 (33.3)			15/36 (41.7)		
CS-resistant	10/18 (55.6)			9/18 (50.0)		
Cumulative dose of CS until initiation of GLM treatment						
≤3,000 mg	9/20 (45.0)	1.519 (0.425, 5.426)	0.5186	12/20 (60.0)	2.786 (0.773, 10.043)	0.1134
>3,000 mg	7/20 (35.0)	1		7/20 (35.0)	1	
Duration of CS use until initiation of GLM treatment						
≤183 days	10/26 (38.5)	1.000 (0.327, 3.057)	1.0000	11/26 (42.3)	1.000 (0.333, 3.005)	1.0000
>183 days	10/26 (38.5)	1		11/26 (42.3)	1	
Prior use of immunomodulators						
No	6/14 (42.9)	1.088 (0.327, 3.618)	0.8912	5/14 (35.7)	0.579 (0.169, 1.977)	0.3798
Yes	20/49 (40.8)	1		24/49 (49.0)	1	
Prior use of biologics						
No	15/27 (55.6)	2.841 (1.005, 8.028)	0.0461	15/27 (55.6)	1.964 (0.714, 5.407)	0.1890
Yes	11/36 (30.6)	1		14/36 (38.9)	1	
1 biologic	7/22 (31.8)	1.167 (0.269, 5.054)	0.8367	7/22 (31.8)	0.467 (0.117, 1.854)	0.2753
≥2 biologics	4/14 (28.6)	1		7/14 (50.0)	1	
1 anti-TNF-α antibody	8/22 (36.4)	1.523 (0.312, 7.442)	0.6015	9/22 (40.9)	0.831 (0.193, 3.576)	0.8033
≥2 anti-TNF-α antibodies	3/11 (27.3)	1		5/11 (45.5)	1	
Prior use of budesonide foam						
No	16/40 (40.0)	0.867 (0.307, 2.450)	0.7872	20/40 (50.0)	1.556 (0.549, 4.409)	0.4046
Yes	10/23 (43.5)	1		9/23 (39.1)	1	
Therapy used immediately before GLM treatment						
CS						
No	12/33 (36.4)	0.612 (0.222,1.692)	0.3429	18/33 (54.6)	2.280 (0.816, 6.371)	0.1132
Yes	14/29 (48.3)	1		10/29 (34.5)	1	
Anti-TNF-α antibodies						
No	20/42 (47.6)	2.121 (0.684, 6.580)	0.1888	20/42 (47.6)	1.363 (0.463, 4.017)	0.5731
Yes	6/20 (30.0)	1		8/20 (40.0)	1	
Vedolizumab						
No	25/57 (43.9)	3.125 (0.328, 29.735)	0.2999	27/57 (47.4)	3.600 (0.379, 34.229)	0.2384
Yes	1/5 (20.0)	1		1/5 (20.0)	1	
Cytapheresis						
No	22/54 (40.7)	0.6875 (0.155, 3.046)	0.6204	24/54 (44.4%)	0.800 (0.181, 3.536)	0.7682
Yes	4/8 (50.0)	1		4/8 (50.0)	1	

Table 2 (continued)

	In the induction phase (at 6–14 weeks)			In the maintenance phase (at 44–60 weeks)		
	CR, *n* (%)	OR 95% CI	*p* value*	CR, *n* (%)	OR 95% CI	*p* value*
Disease activity at initiation of GLM treatment						
Mayo score						
3–7	10/23 (43.5)	0.692 (0.204, 2.347)	0.5544	11/23 (47.8)	1.019 (0.302, 3.438)	0.9764
8–12	10/19 (52.6)	1		9/19 (47.4)	1	
pMayo score						
3–5	14/37 (37.8)	0.710 (0.257, 1.965)	0.5092	17/37 (46.0)	0.992 (0.363, 2.713)	0.9870
6–9	12/26 (46.2)	1		12/26 (46.2)	1	
MES						
0–2	14/30 (46.7)	0.875 (0.229, 3.341)	0.8451	15/30 (50.0)	1.400 (0.362, 5.414)	0.6252
3	6/12 (50.0)	1		5/12 (41.7)	1	
UCEIS						
1–4	8/17 (47.1)	1.086 (0.297, 3.976)	0.9003	8/17 (47.1)	0.727 (0.199, 2.661)	0.6301
5–8	9/20 (45.0)	1		11/20 (55.0)	1	
Matts classification						
2–4	6/14 (42.9)	1.250 (0.289, 5.407)	0.7651	7/14 (50.0)	1.286 (0.305, 5.426)	0.7321
5	6/16 (37.5)	1		7/16 (43.8)	1	
Hb						
<11 g/dL	13/26 (50.0)	1.769 (0.634, 4.938)	0.2741	12/26 (46.2)	0.958 (0.348, 2.634)	0.9337
≥11 g/dL	13/36 (36.1)	1		17/36 (47.2)	1	
Platelet						
$<30 \times 10^4$/μL	12/27 (44.4)	1.200 (0.434, 3.317)	0.7251	16/27 (59.3)	2.462 (0.879, 6.890)	0.0835
$\geq 30 \times 10^4$/μL	14/35 (40.0)	1		13/35 (37.1)	1	
CRP						
<0.3 mg/dL	12/31 (38.7)	0.767 (0.279, 2.108)	0.6067	16/31 (51.6)	1.477 (0.542, 4.025)	0.4451
≥0.3 mg/dL	14/31 (45.2)	1		13/31 (41.9)	1	

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; GLM, golimumab; MES, Mayo endoscopic subscore; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity. *Pearson's correlation coefficient.

GLM treatment was not significant (OR: 0.407, p = 0.1193) (online suppl. Tables S1–3; for all online suppl. material, see https://doi.org/10.1159/000533871).

Next, we investigated the factors associated with CR during the maintenance phase after GLM treatment. In the univariate analysis, no factors at the initiation of GLM treatment were significantly associated with CR (Table 2). Multivariate analysis was performed using disease duration till initiation of GLM treatment, prior biologic use related to GLM response in the induction phase, and cumulative dose of CS that tended to be associated with CR in the univariate analysis (less than 3,000 mg, OR: 2.786, p = 0.1134). In the multivariate analysis, no prior use of biologics was an independent factor associated with CR (OR: 4.221, p = 0.0459) (Table 4). In contrast, disease duration of more than 60 months till initiation of GLM treatment and cumulative dose of CS of less than 3,000 mg were not significant.

Regarding concomitant medications during GLM treatment, patients without concomitant CS showed a significantly higher response to GLM in the maintenance phase (OR: 4.125, p = 0.0112) (online suppl. Table S4). There was no significant association between the concomitant use of other drugs and CR.

GLM Persistence Rate

In our study, the median duration of GLM treatment for 63 patients was 335 days, and 32 patients discontinued GLM after 1 year due to inadequate effectiveness (22 patients), loss to follow-up (4 patients), adverse events (3 patients), remission (2 patients), and patients' choice (1 patient) (Fig. 1). Four patients underwent total colorectal resection for severe UC after discontinuation of GLM. The cumulative probabilities of maintaining GLM treatment after 1 and 2 years were 54.5% and 45.4%, respectively (Fig. 4).

Table 3. Factors related to CR after induction treatment by golimumab, using multivariate logistic regression analysis

	In the induction phase (6–14 weeks)	
	OR 95% CI	*p* value*
Age at diagnosis of UC		
>35 years	2.795 (0.913, 8.556)	0.0717
≤35 years	1	
Duration of disease until initiation of GLM treatment		
>60 months	3.484 (1.042, 11.654)	0.0427
≤60 months	1	
Prior use of biologics		
No	4.221 (1.254, 14.204)	0.0200
Yes	1	

CI, confidence interval; GLM, golimumab; UC, ulcerative colitis. *Pearson's correlation coefficient.

Table 4. Factors related to CR after maintenance treatment by golimumab, using multivariate logistic regression analysis

	In the maintenance phase (44–60 weeks)	
	OR 95% CI	*p* value*
Duration of disease until initiation of GLM treatment		
>60 months	1.869 (0.396, 8.828)	0.4298
≤60 months	1	
Cumulative dose of CS until initiation of GLM treatment		
≤3,000 mg	2.437 (0.617, 9.621)	0.2036
>3,000 mg	1	
Prior use of biologics		
No	4.221 (1.026, 16.189)	0.0459
Yes	1	

CI, confidence interval; GLM, golimumab. *Pearson's correlation coefficient.

Proportion of Patients Maintaining CR

Additionally, we collected data from 17 patients with pMayo scores of ≤2 at the initiation of GLM treatment. The proportions of patients who maintained CR in the induction phase, maintenance phase, and the last follow-up visit were 94.1% (16/17), 69.2% (9/13), and 61.5% (8/13), respectively.

Safety

In all 63 patients, no death or colon cancer/dysplasia was recorded, and one case of renal cancer and two serious infections (cytomegalovirus reactivation and cholecystitis) were recorded during GLM treatment.

Discussion

This retrospective cohort study examined the effectiveness of induction and maintenance treatment with GLM in Japanese patients with UC in clinical practice and the factors associated with CR. We found that the proportions of patients achieving CR during induction and maintenance treatment with GLM were 41.3% and 46.0%, respectively, and biomarker levels gradually improved along with the pMayo score in patients who continued GLM treatment for 1 year. The proportion of patients with CR induction tended to be higher in patients aged >35 years. Furthermore, we found that no biologic use before GLM initiation and disease history of >60 months were significantly associated with a higher proportion of patients achieving CR in the induction phase, and no prior biologic use was significantly associated with a higher proportion of patients achieving CR in the maintenance phase. Despite many reports from overseas on the efficacy of GLM [4–13, 15–19, 21], there have been few studies on the factors that influence the effectiveness of GLM in actual clinical practice in Japan [23]. The clinical factors we have identified in this study regarding GLM treatment of Japanese UC patients are essential for future treatment strategies.

Anti-TNF-α antibody agents available for UC treatment include IFX [28], ADA [29, 30], GLM [2, 3], IFX-BS [31], and ADA-BS [32], and physicians select them based on patients' disease activity and lifestyle. Therefore, it is important to know the actual clinical data, which differs from clinical trials [33]. In Japan, there is one clinical trial on GLM [22] as well as one post-marketing surveillance report [23]; however, there are few clinical research reports. Therefore, we examined the effectiveness, factors associated with response, and safety of GLM treatment in patients with UC using data from a cohort study in Hokkaido, Japan (Phoenix cohort) [34].

First, we found that GLM treatment resulted in a good proportion of patients achieving CR in both the induction and maintenance phases (41.3% and 46.0%, respectively). In addition, the proportion of patients with clinical responses in the induction and maintenance phases was also satisfactory (54.0% and 55.6%, respectively). The PURSUIT-J study [22] showed that 43.8% of patients achieved clinical response and 18.8% achieved CR based on the Mayo score obtained at week 6. In addition, among induction responders, patients receiving GLM treatment

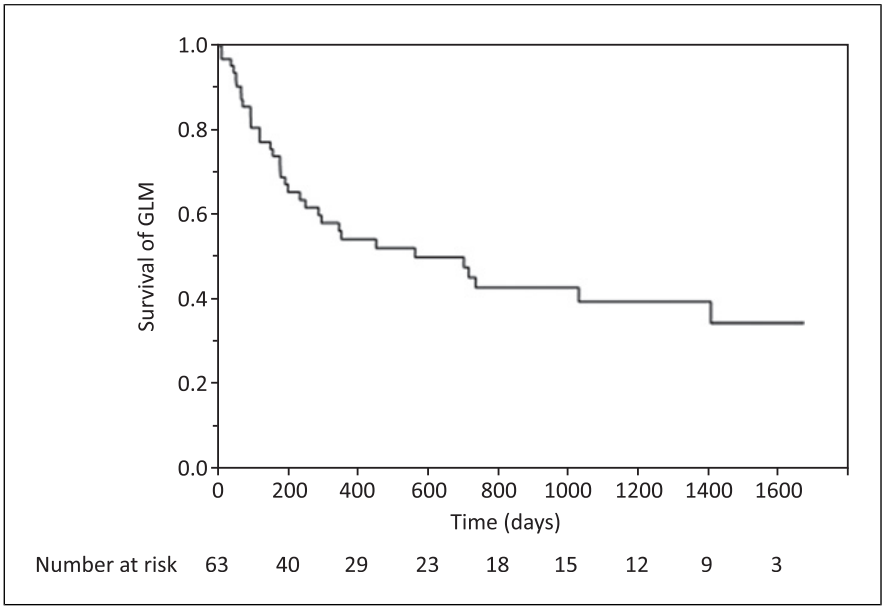

Fig. 4. Kaplan-Meier survival curve showing drug persistence of GLM. GLM, golimumab.

maintained a clinical response of 56.3% and achieved CR based on the Mayo score at 50.0%. Real-life observational studies showed that the proportion of patients achieving CR in the induction phase ranged from 14.3% to 51.5%, while those in the maintenance phase ranged from 17.6% to 49% [4–10, 13, 16, 17, 19–21, 23], although it should be noted that some studies performed GLM dose escalation and the proportion of patients with prior biologic use varied among studies. Taken together, the proportions of patients achieving CR in the induction and maintenance phases obtained in the present cohort data were comparable with those of previous reports, including clinical trials [2, 3, 22] and real-world data [4–10, 13, 16, 17, 19–21, 23].

Next, we examined factors associated with CR during the induction phase of GLM treatment. Regarding factors associated with response to GLM, previous use of anti-TNF-α antibodies, disease duration, and extent of the disease have been reported [5, 7, 8, 13, 19, 21]. The present cohort study indicated that the age of 35 years or older and disease duration of > 60 months may be positive factors for CR induction. Interestingly, these results are inconsistent with previous reports where shorter disease duration and younger age were associated with response to GLM [5, 7, 35]. Several reports have shown that sex and BMI are associated with the trough levels of biologics [25–27]. We performed a multivariate analysis by considering BMI and sex and found that a disease duration of 60 months or more was not significant. The exact reason for this is not clear; however, the background of the enrolled patients may have influenced the results of our study. However, we believe these results indicate the complexity of UC pathogenesis [36]. It is necessary to consider treatment options by identifying the cytokines that contribute to the pathogenesis of each UC patient, regardless of age or disease duration. Additionally, we found a significant association between no prior biologic use and a higher proportion of CR, which is in agreement with previous reports [8, 13].

Taxonera et al. [6] reported that patients with UC refractory to two or more anti-TNF-α antibody agents had a reduced response to treatment with GLM. In contrast, our data showed no difference in treatment responsiveness despite the number of biological agents that patients received. The EVOLVE study [37] demonstrated that the use of anti-TNF-α antibody therapies after VDZ treatment did not affect the response to treatment. Our results may provide important information for future UC treatment strategies.

Generally, to improve the quality of life of patients with IBD, it is important to identify factors contributing to the maintenance of long-term remission. Therefore, we investigated the factors involved in the maintenance phase after GLM treatment. Of note, we found a significant association between no prior use of biologics and CR after maintenance treatment with GLM in multivariate analysis. Several reports indicated that factors associated with long-term remission of UC treated with GLM were the extent of disease and CR at 12 weeks [6, 17, 21]. Pugliese et al. [16] indicated an association between long-term

GLM persistence and no prior use of anti-TNF-α antibody agents, which is consistent with our report.

It is reported that CS influences intestinal epithelial regeneration by suppressing the NF-kappa B pathway [38, 39]. The results of the present study suggest that a cumulative CS dose of 3,000 mg or less may affect GLM response to the maintenance of remission (OR: 2.786, p = 0.1134 in univariate analysis and 2.437, p = 0.2036 in multivariate analysis). This result may indicate the importance of appropriately timed therapeutic interventions, including biologics, in the treatment of refractory UC by considering the total dose of CS.

It is reported that the concomitant use of immunomodulators contributes to endoscopic remission of UC and significantly lower colectomy rate during GLM treatment [6, 40]. On the other hand, we observed no association between concomitant use of immunomodulators and remission with GLM after 1 year. Unfortunately, we could not investigate the effect of concomitant immunomodulators on long-term remission with GLM or endoscopic and histological remission due to the limited number of patients treated with GLM for >1 year and those with endoscopic and histologic assessments in this study. Therefore, further data accumulation will be needed to clarify this issue. Recently, endoscopic remission has been a treat-to-target for the management of UC.

Our study showed that the median duration of GLM treatment in the 63 patients analyzed was 335 days. In addition, GLM persistence rates at 1 and 2 years after initiation were 54.5% and 45.4%, respectively. Other real-world cohort studies of GLM reported that the treatment persistence rates ranged from 44.7% to 63% at 1 year [8, 11, 15–17, 20, 23] and 22.5–46% at 2 years [15, 16]. Thus, the persistence rates of GLM in Japanese patients with UC have a similar tendency to that reported in a previous study.

In terms of safety, no deaths or colon cancer/dysplasia were observed, but 1 patient developed renal cancer and 2 patients had serious infections (cytomegalovirus reactivation and cholecystitis) among the 63 patients during GLM treatment. In a previous report evaluating the GLM safety in the maintenance phase [3], 2.6% of patients developed neoplasm and 3.2% of patients had serious infections in the 100 mg (the approved dose in Japan) treatment group, similar to the present data.

Our study had several limitations. The number of enrolled patients was small and we did not include pediatric cases. If more patients were enrolled, it might be possible to compare the treatment effects by age groups. In addition, the number of patients who received biologics other than anti-TNF-α antibodies prior to GLM was small and we could not analyze its effect. This retrospective study had many missing values, such as endoscopic findings in all enrolled patients and fecal calprotectin. Biomarkers are important in the future management of IBD; therefore, it would be better to follow up on fecal calprotectin values during GLM treatment [41, 42]. Additionally, some pMayo score data in the maintenance phase were missing due to discontinuation of GLM. We imputed it using the LOCF method for patients who discontinued treatment for reasons other than inadequate response; therefore, results in the maintenance phase may be biased.

In conclusion, we demonstrated real-life clinical treatment effectiveness of GLM in Japanese patients with UC and the factors associated with CR. The results suggest that treatment with GLM for the induction and maintenance of CR is beneficial, particularly in biologic-naive patients, and that GLM treatment can also be initiated in patients with long-term disease duration of UC.

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Statement of Ethics

This study complied with the Declaration of Helsinki of the World Medical Association (amended October 2013) and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (partially amended on March 10, 2022). This study was approved by the Ethics Committee of the Sapporo Medical University School of Medicine (approval number 302-101). Because this study was a retrospective analysis of de-identified data, opt-out informed consent protocol was used for use of participant data for research purposes. This consent procedure was approved by the Ethics Committee of the Sapporo Medical University School of Medicine (approval number 302-101, date of decision October 11, 2018).

Conflict of Interest Statement

S.M. has served as a speaker for Takeda, Janssen, Mitsubishi Tanabe, JIMRO, and AbbVie and has received research funding from Janssen, EA Pharma, Takeda, Pfizer, Lilly, AstraZeneca, AbbVie, and Gilead. K.A. has served as a speaker for Mitsubishi Tanabe and Janssen. M.F. has served as a speaker for Takeda, Janssen, Nippon Kayaku, EA Pharma, and AbbVie and has received research funding from Takeda, Nippon Kayaku, Ayumi, Fuji Pharma, EA Pharma, AbbVie, Janssen, and JIMRO and scholarship grant from Mochida. T.I., S.F., and A.M. have received research funding from Janssen. N.S., N.M., and Y.I. are employees of Mitsubishi Tanabe Pharma Corporation. H.N. has served as a speaker for Mitsubishi Tanabe, Janssen, Takeda, AbbVie, Pfizer, Viatris, and Gilead and has received research funding from HOYA and

scholarship grants from AbbVie, Otsuka, EA Pharma, Taiho, Nippon Kayaku, and Mitsubishi Tanabe. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

D.H., N.S., N.M., Y.I., and H.N. developed the study design. D.H., S.M., T.A., K.A., M.F., T.I., S.F., A.M., and T.K. collected data, and D.H. and S.H. analyzed the data. D.H., N.S., and H.N. drafted the manuscript. All authors revised the manuscript and approved the final version of this manuscript.

Data Availability Statement

The data of this study are available on request due to privacy requirements. Further inquiries can be directed to the corresponding author.

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