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Therapeutic Drug Monitoring of Golimumab for the Prediction of Long-Term Clinical Remission in Patients with Ulcerative Colitis

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Keywords
Golimumab · Ulcerative colitis · Therapeutic drug monitoring · Tumor necrosis factor-alpha

Abstract
Background and Aims: A considerable number of patients with ulcerative colitis (UC) who initially respond to golimumab (GLM), an anti-TNF-α antibody, gradually lose clinical response. Therapeutic drug monitoring has been proposed to optimize serum anti-TNF-α antibody concentrations before the loss of response; however, little is known about ideal serum GLM concentrations. We aimed to evaluate whether the serum GLM trough levels (TLs) early after the initiation of induction therapy affect the long-term outcomes in UC and to identify the early GLM TLs that should be targeted for better long-term outcomes. ***Methods:*** Thirty-one patients were prospectively evaluated. The primary outcome was clinical remission at 54 weeks, and we measured the serum GLM TLs at weeks 6, 10, and 14. Receiver operating characteristic (ROC) curves were constructed to identify optimal GLM TL thresholds early after induction therapy that were associated with clinical remission at week 54. ***Results:*** The GLM TL at week 14, but not at weeks 6 or 10, was significantly associated with clinical remission at week 54 (median [IQR] 1.6 [1.3–1.6] μg/mL vs. 0.9 [0.6–1.3] μg/mL; $p = 0.04$). The area under the ROC curve for GLM TLs at week 14 was 0.78. We identified a week-14 GLM TL of 1.1 μg/mL as the target threshold for achieving clinical remission at week 54. ***Conclusion:*** Our results demonstrate the value of early serum GLM TLs in predicting the long-term outcomes of GLM for patients with UC.

Introduction

Golimumab (GLM) is a fully human monoclonal immunoglobulin G1 antibody that inhibits tumor necrosis factor-alpha (TNF-α) and is approved for the treatment of moderate to severe ulcerative colitis (UC). The safety and efficacy of subcutaneous GLM induction therapy were investigated in PURSUIT-SC, a randomized, double-blind, placebo-controlled study [1]. This study showed that, at week 6 (end of the induction phase), the clinical response rate was 51% among pa-

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tients given GLM, compared with 30%, among patients given placebo. The exposure-response relationship was examined further, and it was observed that higher quartiles of serum GLM trough levels (TLs) were associated with greater clinical response and clinical remission rates at week 6 [2]. Magro et al. [3] also reported that TLs at week 6 of GLM treatment correlated not only with clinical response at week 6 but also with endoscopic/histological disease activity and fecal calprotectin levels.

In comparison to PURSUIT-SC, a phase III maintenance study (PURSUIT-M) examined the long-term safety and efficacy of GLM [4]. At week 54, 42.4% of the patients in the GLM 100-mg group were in clinical remission, compared to 26.6% in the placebo group, indicating that GLM was more effective than placebo. However, up to 40% of the patients with UC, who initially responded to GLM, lost clinical response over time. One of the main reasons for loss of response is the pharmacokinetic profile of GLM – lower GLM TLs during maintenance therapy have been associated with loss of response, while higher TLs have been associated with clinical remission [2]. The key may be to determine the pharmacokinetic profile of GLM in the patient and intervene to optimize the target concentration before losing response. Early measurements of drug concentrations may improve outcomes in cases of inefficacy associated with inadequate serum drug concentrations. However, there is a lack of information regarding the possibility to predict early the long-term outcome of patients treated with GLM. The objective of this prospective study was to evaluate whether serum GLM TLs, early after initiation of induction therapy, affect long-term outcomes in UC and to identify clinically relevant TLs that should be targeted for better long-term outcomes.

Materials and Methods

Patients

This prospective, observational study was performed at Osaka Medical and Pharmaceutical University Hospital, from May 2017 to October 2020. The study included consecutive patients with UC who were initiated on GLM therapy (induction therapy) and who fulfilled the following inclusion criteria: age between 18 and 75, with a diagnosis of moderate-to-severe UC. The exclusion criteria were imminent need for surgery, history of malignancy, and any contraindications specified in GLM's product monograph, such as tuberculosis, severe infection, or congestive heart failure. After inclusion and exclusion criteria were applied, a total of 31 patients were enrolled. Induction therapy was from week 0 to 6. Patients were administered 200-mg GLM at week 0, and 100 mg at week 2, subcutaneously. After week 6, maintenance treatment began, which entailed 100 mg of subcutaneous GLM, every 4 weeks. Only enrolled patients who were administered the week-6 100-mg subcutaneous injection were included in this study.

Outcomes

Our primary outcome was clinical remission at week 54. We defined clinical remission as a partial Mayo (pMayo) score of two points or fewer, with each subscore being zero or one. Clinical response was defined as a decrease from baseline score by at least three points, and 30% decrease in the pMayo score, accompanied by a decrease of at least one point in the rectal bleeding score, or a rectal bleeding score of zero. Clinical and laboratory remission was defined as being in clinical remission with a normal C-reactive protein level.

Serum GLM and Anti-GLM Antibody Measurements

GLM TLs were determined using Golimumab ELISA (Matriks Biotechnology Co. Ltd., Ankara, Turkey), with serum samples collected immediately before administration of the third, fourth, and fifth injection (at week 6, 10, and 14, respectively). Anti-GLM antibodies were determined using the qualitative Antibody to Golimumab ELISA Kit (Matriks Biotechnology Co. Ltd.). Anti-GLM antibody status (detectable or not detectable) could only be reported qualitatively. This assay did not allow for the detection of antidrug antibodies in the presence of GLM. We evaluated anti-GLM antibodies in serum samples obtained at week 14.

Statistical Analysis

All statistical analyses were performed using the JMP v15.2.1 software (SAS Institute, Cary, NC, USA). Quantitative data were summarized using median and interquartile range [IQR], and categorical variables were described using frequency and percentage. We used the Wilcoxon signed-rank test for the comparison of the serum GLM TLs between the patients who achieved and did not achieve the specified efficacy outcomes. The Cochrane-Armitage test for trend was used for trend analysis in GLM TLs quartile data. Receiver operating characteristic (ROC) curves were constructed to find the best sensitivity and specificity cut-off values of GLM TL, at early time points, for the prediction of outcomes at week 54. Moreover, ROC curves were used to identify cut-off prevalence-adjusted positive and negative predictive values (PPV and NPV, respectively). Kaplan-Meier survival analysis plots and log-rank tests were used to compare GLM termination rates between the study arms. Statistical significance was set as $p < 0.05$ (two-sided test).

Results

Patient Characteristics

Twenty-six (out of 31) patients completed the induction phase (week 1–6). The two reasons for patient discontinuation from the study were the lack of treatment efficacy ($n = 2$) and protocol violation ($n = 3$). Table 1 shows the baseline demographics and clinical characteristics of the 26 patients. The median age was 51.5 years and 53.8% of the patients were male. The median [IQR]

Table 1. Baseline demographics and clinical characteristics

Patients, *n*	26
Male/female, *n*	14/12
Age, median (IQR), years	51.5 (33.3–63.8)
Weight, median (IQR), kg	57.2 (52.3–69.2)
Duration of disease, median (IQR), years	1.3 (0.7–8.8)
UC location, left side/extensive, *n*	7/19
Concomitant 5-aminosalicylic acid, *n* (%)	22 (84.6)
Concomitant immunomodulator, *n* (%)	9 (40.9)
Corticosteroids, *n* (%)	18 (69.2)
History of treatment failure with biologics, *n* (%)	1 (3.8)
Partial Mayo score, median (IQR)	7 (5–8)
WBC, median (IQR), /μL	7,890 (4,595–10,055)
Hb, median (IQR), g/dL	12.5 (11.5–14.0)
Platelet, median (IQR), 10^4/μL	30.1 (25.1–36.8)
Albumin, median (IQR), g/dL	3.9 (3.5–4.2)
CRP, median (IQR), mg/L	0.35 (0.06–2.17)

UC, ulcerative colitis; WBC, white blood cell; CRP, C-reactive protein; IQR, interquartile range.

duration of UC was 1.3 [0.7–8.8] years. The percentage of patients with UC with extensive disease was 73.1%. Eighteen patients (69.2%) were on corticosteroids at the start of GLM treatment, and 9 patients (34.6%) were taking an immunosuppressive drug as concomitant medication. Twenty-five of the patients were bio-naïve and only one was bio-switched from adalimumab. The median [IQR] pMayo score was 7 [5–8].

Clinical Response

Fourteen patients (53.8%) responded to induction therapy at week 6: 4 patients (15.4%) showed clinical response, and 10 (38.5%) achieved clinical remission. Seven patients discontinued GLM by week 14, owing to the lack of efficacy. At week 54, 8 patients (30.8%) had sustained clinical remission, while 5 patients (19.2%) had lost response. Of the 17 patients with GLM failure, 12 were switched to infliximab (IFX) and 6 (50%) achieved clinical remission. Two patients were switched to tofacitinib, and both achieved clinical remission. One patient was switched to vedolizumab but did not respond. One patient was treated with 5-aminosalicylic acid suppositories and one with oral prednisolone in combination with GLM, and both achieved clinical remission. A total of 69 samples from 26 patients were analyzed at 6, 10, and 14 weeks, for 26, 24, and 19 patients, respectively.

Relationship between Serum GLM TL and Treatment Outcomes

First, we examined the relationship between GLM TLs and the effectiveness of GLM at the end of the induction phase and early in the maintenance phase. GLM TLs were similar between the patients in clinical remission ($n = 10$) and patients not in clinical remission ($n = 16$) at week 6 (median [IQR] 1.9 [1.4–2.5] μg/mL, vs. 1.2 [0.9–2.6] μg/mL, $p = 0.268$) (Fig. 1a). In contrast, GLM TLs were significantly associated with clinical remission at week 10 (median [IQR] 1.7 [1.3–2.4] μg/mL for patients in clinical remission [$n = 10$] vs. 1.0 [0.7–1.2] μg/mL for patients not in clinical remission [$n = 14$], $p = 0.027$) (Fig. 1c). At week 14, 11 patients (42.3%) were in clinical remission and 12 patients (46.2%) were nonresponders. GLM TLs were significantly associated with clinical remission at week 14 (median [IQR] 1.5 [1.2–2.0] μg/mL for patients in clinical remission, and 0.8 [0.6–1.0] μg/mL for patients not in clinical remission, $p = 0.041$) (Fig. 1e). Next, we examined the relationship between GLM TLs and "clinical and laboratory remission" at weeks 6 (Fig. 1b), 10 (Fig. 1d), and 14 (Fig. 1f). GLM TLs were significantly associated with clinical and laboratory remission at week 14 only (median [IQR] 1.5 [1.2–2.0] μg/mL for patients in clinical and laboratory remission ($n = 10$) vs. 0.6 [0.4–0.9] μg/mL for patients not in clinical and laboratory remission ($n = 9$), $p = 0.002$) (Fig. 1f).

Predictive Value of Post-Induction GLM TLs

Serum GLM TLs at weeks 6, 10, and 14 were compared between the patients in clinical remission and nonremission at week 54. All patients who were in clinical remission at week 54 had normal C-reactive protein levels. GLM TLs at week 6 and week 10 were not associated with clinical remission at week 54 (median [IQR] week 6: 2.3

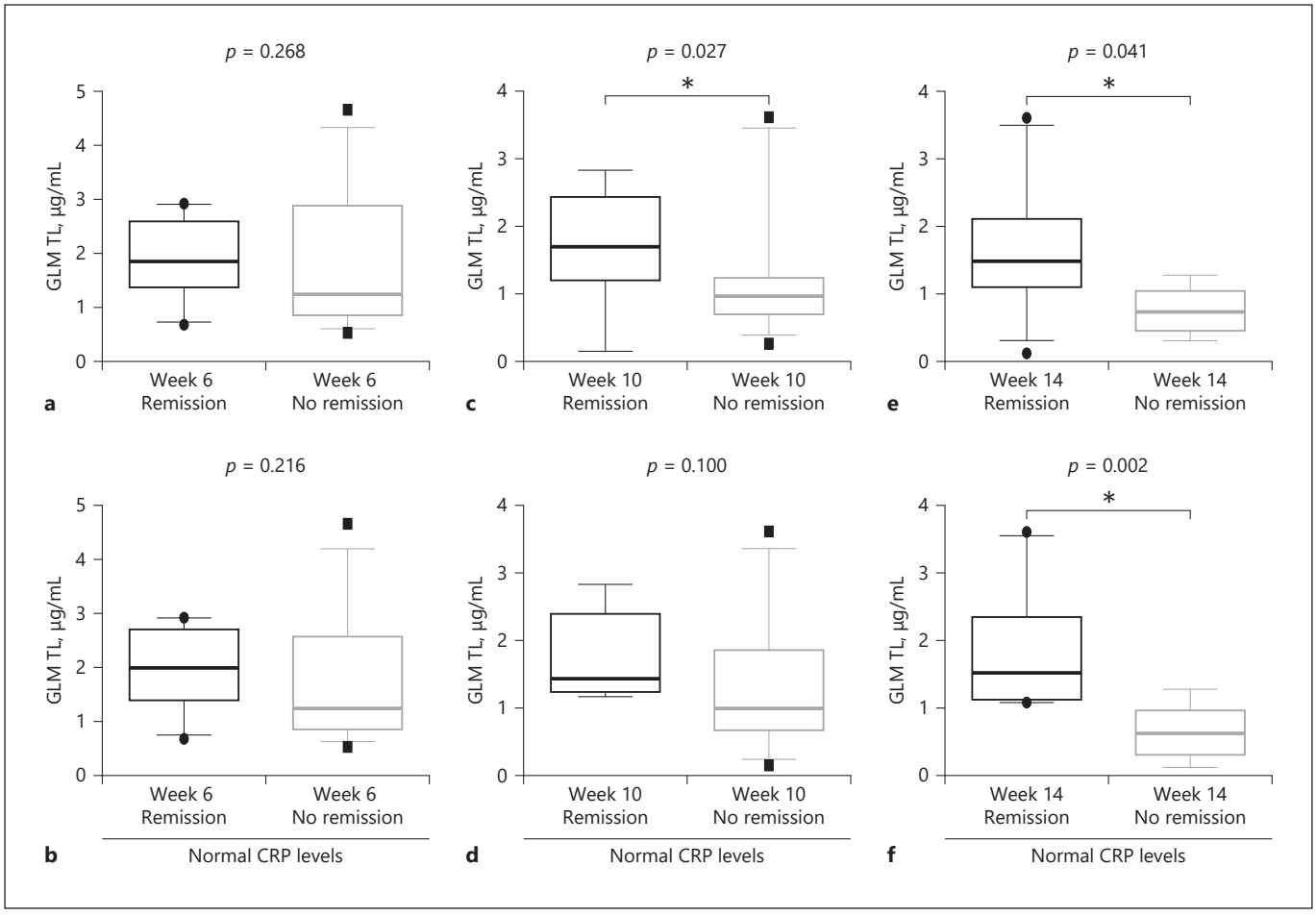

Fig. 1. Relationship between serum GLM TLs and clinical efficacy at week 6 (**a**, **b**), week 10 (**c**, **d**), and week 14 (**e**, **f**). The bold horizontal line represents the median value. CRP, C-reactive protein.

[2.0–2.6] μg/mL for the patients in clinical remission vs. 1.3 [0.8–2.0] μg/mL for patients not in clinical remission, $p = 0.110$; week 10: 1.9 [1.3–2.4] μg/mL for patients in clinical remission vs. 1.0 [0.7–1.6] μg/mL for patients not in clinical remission, $p = 0.205$) (Fig. 2a, c). However, the serum GLM TLs at week 14 were significantly associated with clinical remission at 54 weeks of treatment (median [IQR] 1.6 [1.3–1.6] μg/mL vs. 0.9 [0.6–1.3] μg/mL, $p = 0.043$) (Fig. 2e). Similarly, the GLM TLs at week 14 were also significantly higher in clinical response patients at week 54, than those who were not in response (median [IQR] 1.6 [1.4–1.8] μg/mL vs. 0.8 [0.6–1.0] μg/mL, $p = 0.009$) (Fig. 2f). These results suggest that the long-term outcome is associated with the GLM TL of week 14, but not with the GLM TL of week 6 or week 10, possibly because it is too early in treatment for TL analysis.

To further investigate the exposure-response relationship, quartile analysis was carried out at week 14 (Fig. 3). The proportions of patients achieving efficacy outcomes increased with increasing GLM TLs ($p = 0.0002$ for clinical response at week 54 and $p = 0.076$ for clinical remission at week 54).

Serum Anti-GLM Antibody Status and Associated Therapeutic Response

At week 14, 3 patients (11.5%) had detectable anti-GLM antibodies. There was no significant difference in the positive detection of anti-GLM antibodies between the patients in remission and nonremission at week 14 (1 [9.1%] out of the 11 patients vs. 2 [13.3%] out of 15 patients, $p = 0.738$). There was also no significant difference in the positive detection of anti-GLM antibodies at week 14 between remission and nonremission patients at week

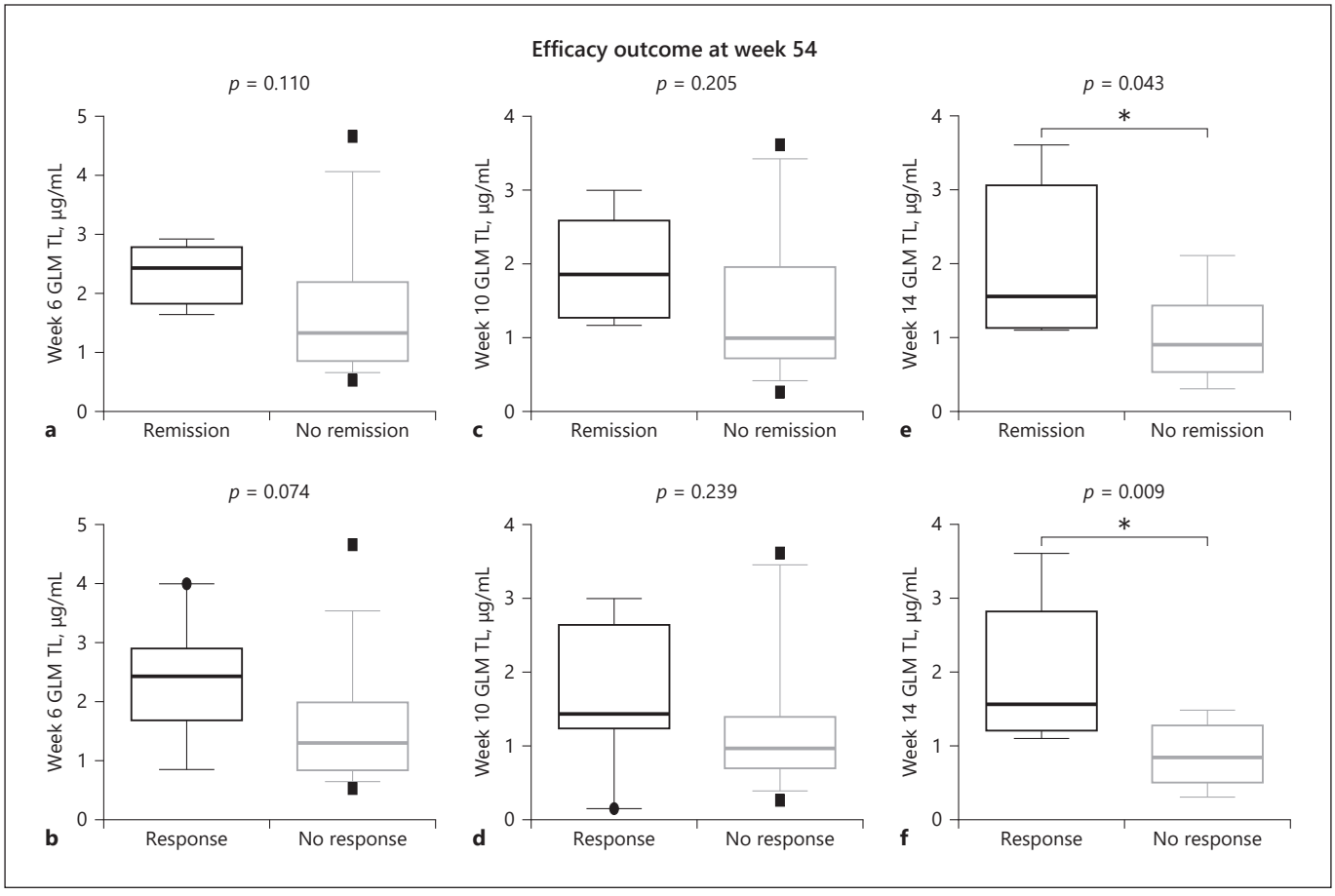

Fig. 2. Relationship between serum GLM TLs, early after the induction phase, and clinical efficacy at week 54. Week 6 (**a**, **b**); week 10 (**c**, **d**); week 14 (**e**, **f**). The bold horizontal line represents the median value.

54 (1 [12.5%] out of 8 patients vs. 2 [11.1%] out of the 18 patients, $p = 0.574$).

ROC Curve Analyses

ROC curves were generated to identify the optimal serum GLM TL thresholds early after induction that were associated with the long-term clinical improvement in UC. Figure 4a shows the ROC curve for GLM TLs at week 14, with an endpoint of clinical remission at week 54. The area under the ROC curve for GLM TLs at week 14 was 0.78 (95% confidence interval, 0.54–1) with moderate accuracy (0.7–0.9). For clinical remission at week 54, the threshold GLM TL of 1.1 µg/mL at week 14 was associated with a sensitivity, specificity, PPV and NPV of 87.5%, 62.5%, 70% and 83.3%, respectively. Similarly, the ROC curve for GLM TLs at week 14 was generated, with an endpoint of clinical response at week 54 (Fig. 4b), and the area under the ROC curve was 0.87 (95% confidence interval, 0.70–1), also with moderate accuracy. The optimal GLM TL threshold at week 14 was 1.1 µg/mL, which was the same as the clinical remission endpoint, and the sensitivity value, specificity value, PPV, and NPV were 88.9%, 71.4%, 80%, and 83.3%, respectively.

Kaplan-Meier Curve Analyses

Figure 5 depicts the survival analysis of time to treatment termination. Nineteen patients who received the week-14 injection were included in this analysis. The analysis was divided into patients whose GLM TLs exceeded the optimal GLM week-14 TL target threshold of 1.1 µg/mL and those whose GLM TLs did not. GLM termination rate by week 54 was significantly lower in the >1.1 group compared with the <1.1 group ($n = 11$, 27.3% vs. $n = 8$, 87.5%, respectively, $p = 0.033$). The median time to GLM termination was significantly longer in the >1.1 group compared with the <1.1 group ($p = 0.006$).

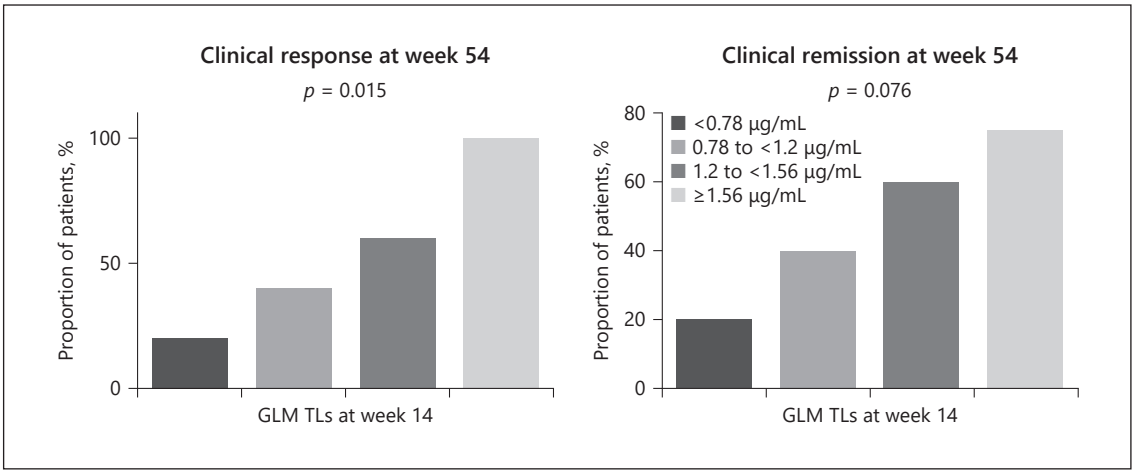

Fig. 3. Proportion of patients in clinical response and clinical remission according to GLM TLs quartile at week 14.

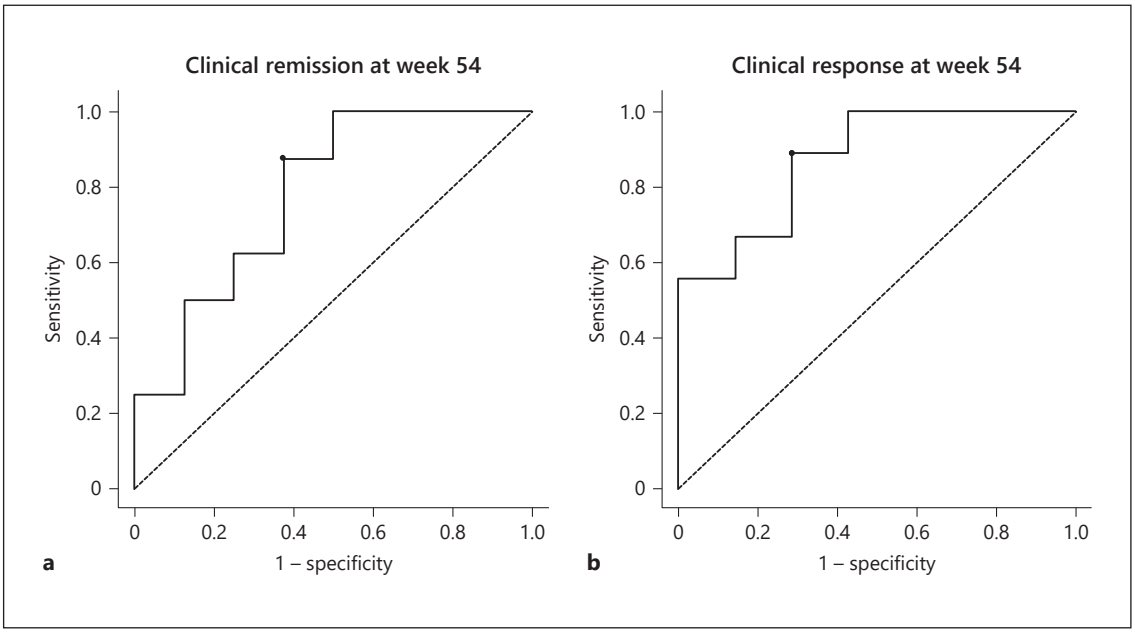

Fig. 4. ROC curve analysis of optimal serum GLM TL thresholds at week 14 associated with clinical remission (**a**) and clinical response (**b**) at week 54.

Demographics and Clinical Characteristics Associated with Clinical Remission and GLM TLs

We examined clinical factors associated with clinical remission at week 54. As shown in Table 2, no baseline factors were associated with clinical remission at week 54. On the other hand, pMayo score, albumin, and platelet at week 14 were significantly associated with clinical remission at week 54 ($p = 0.003$, 0.031, and 0.047, respectively). Finally, we examined clinical factors associated with GLM TL at week 14 (Table 3). pMayo score and albumin were significantly associated with GLM TL at week 14 ($p = 0.001$ and 0.031, respectively).

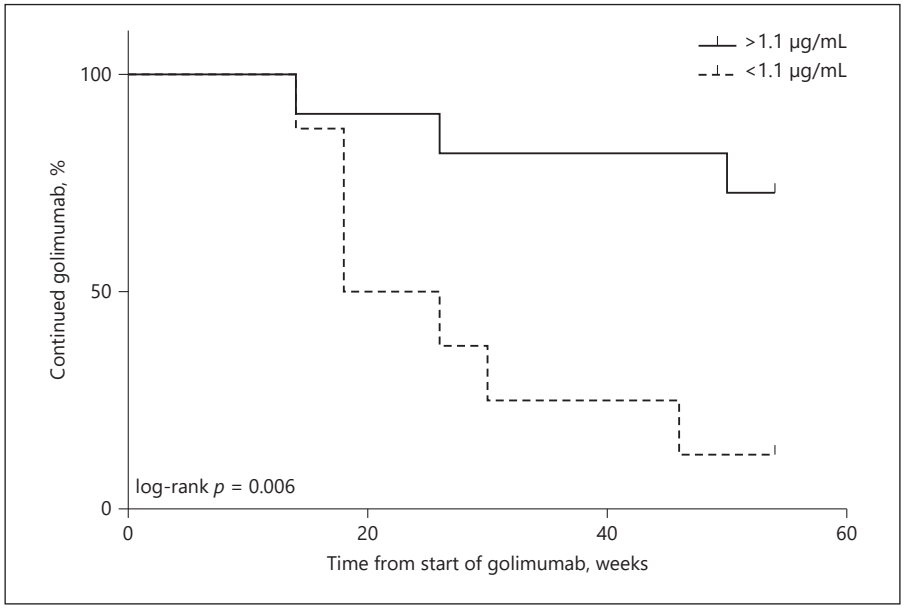

Fig. 5. Kaplan-Meier curve analysis showing treatment termination over time for patients whose serum TLs exceeded the optimal GLM week-14 TL threshold of 1.1 μg/mL and patients whose TLs did not exceed the optimal GLM week-14 TL threshold.

Table 2. Demographics and clinical characteristics

	Remission at week 54	Nonremission at week 54	*p* value
Baseline			
Patients, *n*	8	18	
Male/female, *n*	5/3	9/9	0.555
Age, median (IQR), years	48.5 (41.5–55.5)	58 (33.3–64)	0.505
Weight, median (IQR), kg	56.8 (52.5–58.5)	62.2 (52.5–70)	0.597
Duration of disease, median (IQR), years	6.7 (1.2–19.3)	1.2 (0.8–7.3)	0.211
UC location, left side/extensive, *n*	3/5	4/14	0.418
Concomitant immunomodulator, *n* (%)	4 (50)	5 (27.8)	0.272
Partial Mayo score, median (IQR)	6 (3–6.5)	7 (5.3–8)	0.128
WBC, median (IQR), /μL	8,135 (3,940–9,635)	7,890 (5,312–10,445)	0.803
Hb, median (IQR), g/dL	12.9 (11.9–14.8)	12.4 (11.5–13.5)	0.331
Platelet, median (IQR), 10^4/μL	31.6 (22.4–35.8)	29.4 (25.3–36.5)	0.978
Albumin, median (IQR), g/dL	4.0 (3.7–4.2)	3.8 (3.4–4.2)	0.486
CRP, median (IQR), mg/L	0.33 (0.05–1.47)	0.18 (0.10–1.83)	0.934
Week 14			
Patients, *n*	8	11	
Male/female, *n*	5/3	6/5	0.729
Age, median (IQR), years	48.7 (41.7–55.7)	59.2 (33.7–67.7)	0.508
Duration of disease, median (IQR), years	6.9 (1.4–19.5)	2.1 (1.0–8.3)	0.385
UC location, left side/extensive, *n*	3/5	1/10	0.134
Concomitant immunomodulator, *n* (%)	4 (50)	2 (18.2)	0.141
Partial Mayo score, median (IQR)	0 (0–1.3)	4.5 (2.3–6)	0.003
WBC, median (IQR), /μL	4,515 (4,273–5,508)	5,390 (4,295–7,855)	0.433
Hb, median (IQR), g/dL	13 (12.6–14.8)	12.1 (10.7–13.3)	0.342
Platelet, median (IQR), 10^4/μL	20.3 (18.0–27.1)	30.2 (24.3–34.2)	0.047
Albumin, median (IQR), g/dL	4.2 (4.0–4.5)	3.6 (3.4–3.9)	0.031
CRP, median (IQR), mg/L	0.03 (0.01–0.05)	0.35 (0.18–0.85)	0.098

UC, ulcerative colitis; WBC, white blood cell; CRP, C-reactive protein; IQR, interquartile range.

Table 3. Demographics and clinical characteristics at week 14

	High TL (>1.1 μL/mL)	Low TL (<1.1 μL/mL)	*p* value
Patients, *n*	11	8	
Male/female, *n*	5/6	6/2	0.198
Age, median (IQR), years	50 (37–61)	53.5 (33.8–66.5)	0.563
Duration of disease, median (IQR), years	3.6 (1.5–13.3)	3.3 (1.1–9)	0.508
UC location, left side/extensive, *n*	3/8	1/7	0.435
Concomitant immunomodulator, *n* (%)	4 (36.4)	2 (25)	0.599
Partial Mayo score, median (IQR)	0 (0–2)	6 (3–6)	0.001
WBC, median (IQR), /μL	4,560 (4,215–5,865)	5,965 (4,698–9,673)	0.231
Hb, median (IQR), g/dL	12.8 (12–13.9)	12.3 (10.3–14.3)	0.591
Platelet, median (IQR), 10^4/μL	24.7 (18.7–28.3)	31.5 (23.5–35.0)	0.117
Albumin, median (IQR), g/dL	4.0 (3.9–4.4)	3.5 (3.3–3.8)	0.031
CRP, median (IQR), mg/L	0.03 (0.02–0.05)	0.63 (0.32–0.96)	0.052

TL, trough level; UC, ulcerative colitis; WBC, white blood cell; CRP, C-reactive protein; IQR, interquartile range.

Discussion

This is the first prospective study to evaluate the association between GLM TLs, early after initiation of induction therapy, and long-term outcomes of GLM treatment in patients with UC. We showed that the patients who achieved clinical remission at week 54 demonstrated significantly higher GLM TLs at week 14, compared to the patients who were not in clinical remission at week 54. It has been reported that several UC patients who are treated with GLM show a loss of response during the course of the treatment [1, 4]. Therefore, predicting long-term outcomes using GLM TLs using early responses during the course of treatment may be clinically valuable in determining the appropriate therapeutic interventions to prevent a loss of response. Although there are limited reports on the exposure-response relationships during GLM maintenance therapy, a loss of response may be caused by insufficient exposure to the drug because higher GLM TLs are associated with clinical remission [2]. In the present study, 6 (42.9%) out of 14 patients who responded at week 6 showed loss of response by week 54. A GLM w14 TL of 1.1 μg/mL was the target threshold for achieving clinical remission at week 54, with a sensitivity of 87.5% and a specificity of 62.5%. Furthermore, the GLM termination rate by week 54 was 27.3% in the patients with GLM TLs of 1.1 μg/mL or higher at week 14, which was significantly lower than the termination rate of 87.5% in patients with GLM TLs of less than 1.1 μg/mL ($p = 0.01$).

GLM TLs at week 10 were significantly higher in patients in clinical remission at week 10, compared with the TLs of patients not in remission, but TLs at week 10 were not associated with remission at week 54. As the serum GLM is reported to reach steady-state TL at week 14 [2, 5], if GLM concentrations are already low at week 14, it is likely that this pharmacokinetic profile will not change. Therefore, our finding that GLM w14 TL is associated with long-term clinical outcomes is reasonable. Furthermore, in the PURSUIT-M study analysis, the target threshold TL for maintenance of steady-state response was identified as 1.4 μg/mL. In the present study, the target threshold of GLM TL at week 14 was similar, at 1.1 μg/mL, which supports the findings of the PURSUIT-M study.

A strong association between the TLs and treatment efficacy has also been reported for IFX, an anti-TNF-α monoclonal antibody [6, 7]. Additionally, it has been reported that the IFX TLs at an early time point during the course of treatment is predictive of the long-term IFX efficacy [8–11]. Therapeutic drug monitoring of anti-TNF-α antibodies may be a desirable strategy in the management of patients with inflammatory bowel disease (IBD). However, the question of whether treatment efficacy can be attained or regained by increasing the dosages of anti-TNF-α antibodies, in patients who have low serum drug concentrations, remains unanswered. Mixed results have been reported by studies that examined IFX TL-guided therapy [12–14]. Several IBD guidelines mention the possibility of using therapeutic drug monitoring of anti-TNF-α antibodies in guiding treatment in the fu-

ture, but these guidelines do not make any recommendations at present [15–17]. For GLM, prospective studies are needed to investigate dose titration for patients with low serum drug concentrations, with the goal of exceeding the identified TL threshold.

In this study, GLM TLs were significantly associated with clinical remission at week 14 and more significantly with clinical and laboratory remission. In addition, GLM TLs were significantly associated with pMayo score and albumin at week 14. This suggests that low GLM TLs may not suppress inflammation at early stages after the initiation of induction therapy. On the other hand, pMayo score, albumin, and platelet at week 14 were significantly associated with clinical remission at week 54. In general, the maintenance of remission is known to be related not only to the serum drug concentration but also to the clinical factors in the treatment of IBD with anti-TNF-α antibodies [18–21]. We showed that not only GLM TLs but also disease activity at week 14 are associated with long-term outcomes in UC.

The current study used a drug resistance-free assay and found that anti-GLM antibodies were present in 4 (15.4%) out of the 26 patients at week 14 of treatment [22]. The presence of anti-GLM antibodies was not associated with the efficacy of GLM at week 14 or in the long term. This result is consistent with previous reports, suggesting that immunogenicity may not play an important role in GLM efficacy. However, due to the small number of cases and the use of a drug-resistant immunoassay, it is not possible to conclusively prove causality.

This study has some limitations. First, the sample size was relatively small. Therefore, multivariate analysis could not be performed to analyze whether the GLM TL at week 14 was an independent factor to predict the outcome at week 54. Second, as endoscopic remission was not the primary endpoint, GLM outcomes at week 54 may have appeared to be improved. Third, the assays used to measure GLM TLs and anti-GLM antibodies in this study are commercially available, but caution should be exercised when comparing the target thresholds between studies, as the measurements cannot be directly compared if different assays are used to obtain these measurements.

Conclusion

We explored the relationship between early GLM TLs and long-term outcomes in UC patients. Our results show that a GLM w14 TL threshold of 1.1 μg/mL is predictive of clinical remission at week 54. Further studies are needed to assess the value of proactive therapeutic drug monitoring and dosage adaptation, based on post-induction phase TLs, in predicting long-term GLM efficacy.

Statement of Ethics

This study was performed according to the principles of the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (No. 2804). Written informed consent was obtained from each patient included in this study.

Conflict of Interest Statement

Shiro Nakamura reports receiving speaking fees from AbbVie GK, EA Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation., Mochida Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd, and Janssen Pharmaceutical K.K. Dr. Shinya Fukunishi is an Associate Editor of "Digestion."

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Author Contributions

Hideki Tawa collected data and wrote the initial draft of the manuscript. Kazuki Kakimoto designed the study and interpreted the data and drafted the manuscript. Keijiro Numa, Naohiko Kinoshita, Yuka Kawasaki, Yoshihiro Tatsumi, Ryoji Koshiba, Satoshi Nakata, Yuki Hirata, Kazuhiro Ota, Naokuni Sakiyama, Yuichi Kojima, Eiko Koubayashi, Hiroki Nishikawa, Toshihisa Takeuchi, Takuya Inoue, Shinya Fukunishi, Takako Miyazaki, Shiro Nakamura, and Kazuhide Higuchi have contributed to data collection and interpretation and have critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data are not publicly available because there is no appropriate site for uploading at present. The data underlying this article will be shared on reasonable request to the corresponding author.

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