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Real-World Effectiveness and Safety of Carotegrast Methyl in Japanese Patients with Moderately Active Ulcerative Colitis

Toshihide Ohmori

Department of Gastroenterology, Ohmori Toshihide Gastro-intestinal Clinic, Ageo, Saitama, Japan

Keywords
Inflammatory bowel disease · Observational study · Ulcerative colitis · Carotegrast methyl · Oral alpha 4-integrin antagonist

Abstract

Introduction: Carotegrast methyl (CGM) is an oral, small-molecule α4-integrin antagonist, which became clinically available in Japan in May 2022. CGM is approved for remission induction treatment for moderately active ulcerative colitis (UC) with an inadequate response or intolerance to 5-aminosalicylates. ***Methods:*** We performed a single-center, retrospective, observational study of Japanese patients with moderately active UC to assess the real-world effectiveness and safety of CGM as remission induction treatment. ***Results:*** Of 14 patients, 71% (10/14) were women, and the median (range) age was 47 (20–68) years. Disease types were proctitis in 7% (1/14), left-sided colitis in 50% (7/14), and total colitis in 43% (6/14). With a median (range) treatment duration of 8 (2–26) weeks, the rate of endoscopic improvement (Mayo endoscopic subscore [MES] of 0 or 1) was 64% (9/14), and the rate of endoscopic remission (MES of 0) was 57% (8/14). After treatment with CGM, the median (range) MES decreased significantly from 3.0 (2–3) to 0.0 (0–3) (p = 0.008), the Mayo score decreased significantly from 7.0 (5–9) to 0.0 (0–9) (p = 0.006), and the clinical activity index decreased significantly from 6.0 (1–11) to 0.0 (0–9) (p = 0.015). Stool and diarrhea frequencies decreased significantly after initiating CGM, and the percentage of patients with bloody stool and abdominal pain tended to decrease. The cumulative relapse-free rate at week 26 among 9 patients who achieved endoscopic improvement with CGM was 77.8% (95% confidence interval, 36.5%–93.9%). No adverse drug reactions, including progressive multifocal leukoencephalopathy, were reported during the study period. ***Conclusion:*** This single-center, retrospective, observational study of 14 Japanese patients with UC showed that CGM was safe and effective as a remission induction treatment for moderately active UC with an inadequate response to 5-aminosalicylates in real-world settings.

Introduction

Ulcerative colitis (UC) and Crohn's disease are 2 conditions that are referred to as inflammatory bowel disease (IBD). UC is characterized by idiopathic, continuous inflammation in the colon that extends proximally from the rectum and causes bloody diarrhea and abdominal pain [1]. A previous study showed that 40% of patients had left-sided colitis, 31% had extensive colitis, and 29% had proctitis at UC diagnosis [2]. Most patients with mild to moderate UC are treated with 5-aminosalicylates (5-ASA), which are often continued as maintenance treatment in those who achieve remission

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

Correspondence to:
Toshihide Ohmori, toshihideo@gmail.com

[3]. Novel biologic agents and oral small molecules targeting different points in the pathogenesis signaling pathways have been approved or are being developed to treat patients with IBD [4, 5].

Carotegrast methyl (CGM) is an oral, small-molecule α4-integrin antagonist developed in Japan [6]. CGM exerts its anti-inflammatory effect by selectively inhibiting the binding of α4β1 integrin to vascular cell adhesion molecule 1 (VCAM-1) and α4β7 integrin to mucosal addressin cell adhesion molecule 1 (MAdCAM-1), resulting in reduced lymphocyte migration through the vascular endothelium and lymphocyte infiltration in the inflamed colon [6].

The efficacy and safety of CGM as remission induction treatment for patients with moderately active UC were confirmed in phase 2 [7] and phase 3 [8] studies performed in Japan. In a double-blind, placebo-controlled, phase 3 study of 203 Japanese patients with moderately active UC and an inadequate response or intolerance to mesalazine, patients assigned to receive CGM (960 mg, 3 times a day) had a significantly higher rate of endoscopic improvement (Mayo endoscopic subscore [MES] of 0 or 1) and endoscopic remission (MES of 0) at week 8 compared with patients assigned to receive a placebo [8]. In Japan, CGM was approved in March 2022 and became clinically available in May 2022 as remission induction treatment for patients with moderately active UC who had an inadequate response or intolerance to 5-ASA.

Before the development of CGM, Japanese treatment guidelines for UC recommended short-term oral corticosteroid therapy (prednisolone, 30–40 mg/day) for patients with moderately active UC who had an inadequate response to 5-ASA [9]. A previous study showed that inappropriate long-term use of corticosteroids was common, especially among those who were treated with a low initial dose (<10 mg/day) [10]. Moreover, intolerance to 5-ASA has increased recently among patients with UC, from 5.3% between 2007 and 2010 to 16.2% between 2014 and 2016 [11]. Additionally, the risk of colectomy was reported to be higher in patients intolerant to 5-ASA (11.5%) than that in those who were tolerant (2.6%) [12]. Therefore, there is a growing need for treatment options other than corticosteroids for patients with UC and an inadequate response or intolerance to 5-ASA.

We performed a single-center, retrospective, observational study of 14 Japanese patients with moderately active UC to assess the real-world effectiveness and safety of CGM as a remission induction treatment. We also evaluated the maintenance treatment and relapse status of the patients after discontinuing CGM.

Methods

Study Design and Patients

This was a retrospective observational study to assess the effectiveness and safety of CGM as remission induction treatment in patients with moderately active UC who had an inadequate response to 5-ASA. We collected information on endoscopic improvement from all patients treated with CGM (960 mg, 3 times a day) at Ohmori Toshihide Gastro-intestinal Clinic between May 2022 and December 2022. We then collected information up to September 2023 on maintenance treatment and relapse status in patients who achieved endoscopic improvement with CGM and on subsequent remission induction treatment and outcomes in those who did not achieve endoscopic improvement with CGM. Information on adverse drug reactions (ADRs; adverse events for which a causal relationship to CGM was not ruled out by the treating physician), including progressive multifocal leukoencephalopathy (PML), was collected throughout the entire study period.

Data Collection

We assessed the following patient baseline characteristics: sex, age, body mass index, smoking history, disease duration, disease status (new onset or relapse), UC type (proctitis, left-sided colitis, or total colitis), recent UC treatment, concomitant UC treatment, prior treatment with oral corticosteroids, and MES/Mayo score/clinical activity index (CAI) [13]/endoscopic findings before starting CGM treatment.

We assessed the following during CGM treatment: (i) MES/Mayo score/CAI/endoscopic findings at remission assessment (if there were multiple endoscopic evaluations, the latter was used), (ii) items in the symptoms diary (stool and diarrhea frequencies and episodes of bloody stool and abdominal pain), and (iii) ADRs.

We assessed the following after discontinuing CGM treatment: (i) maintenance treatment and whether there was a relapse (if yes, we recorded the time from endoscopic improvement to relapse, subsequent remission induction treatment, and outcomes) in patients who achieved endoscopic improvement with CGM; (ii) subsequent remission induction treatment and outcomes in those who did not achieve endoscopic improvement with CGM; and (iii) ADRs in all patients. In this study, relapse was defined as deteriorated disease status requiring treatment change or intensification, such as an increase in stool frequency by 3–4 times per day from that in remission or any bloody or mucus stool episode.

Table 1. Patient baseline characteristics

	Overall	Endoscopic improvement[a]	No endoscopic improvement[b]	*p* value
	N = 14	*N* = 9	*N* = 5	
Sex, female	10 (71)	7 (78)	3 (60)	0.580[c]
Age, years	47 (20–68)	50 (24–68)	20 (20–48)	0.052[d]
BMI, kg/m^2	23.6 (19–29)	21.5 (19–29)	24.3 (21–27)	0.257[d]
Smoking history				
No	14 (100)	9 (100)	5 (100)	0.580[c]
Disease duration, years				
<1	1 (7)	0 (0)	1 (20)	0.528[c]
1 to <5	6 (43)	4 (44)	2 (40)	
≥5	7 (50)	5 (56)	2 (40)	
Disease status				
New onset	1 (7)	0 (0)	1 (20)	0.357[c]
Relapse	13 (93)	9 (100)	4 (80)	
UC type				
Proctitis	1 (7)	1 (11)	0 (0)	0.371[c]
Left-sided colitis	7 (50)	3 (33)	4 (80)	
Total colitis	6 (43)	5 (56)	1 (20)	
Recent treatment				
Oral 5-ASA and sulfasalazine				
5-ASA, MMX	12 (86)	8 (89)	4 (80)	0.604[c]
5-ASA, granules	1 (7)	1 (11)	0 (0)	
Sulfasalazine	1 (7)	0 (0)	1 (20)	
Topical treatment				
None	9 (64)	6 (67)	3 (60)	0.580[c]
5-ASA, suppositories	2 (14)	2 (22)	0 (0)	
5-ASA, enemas	2 (14)	1 (11)	1 (20)	
Corticosteroids, enemas	1 (7)	0 (0)	1 (20)	
Immunosuppressants				
None	12 (86)	8 (89)	4 (80)	1.000[c]
Azathioprine	2 (14)	1 (11)	1 (20)	
Prior treatment with oral corticosteroids				
Prednisolone	2 (14)	1 (11)	1 (20)	1.000[c]
MES[e]				
0	0 (0)	0 (0)	0 (0)	1.000[c]
1	0 (0)	0 (0)	0 (0)	
2	4 (36)	3 (38)	1 (33)	
3	7 (64)	5 (63)	2 (67)	
Mayo score[e]	7.0 (5–9)	7.5 (5–9)	7.0 (7–8)	1.000[d]
Clinical activity index	6.0 (1–11)	6.0 (4–7)	5.0 (1–11)	0.486[d]

Values are given as *n* (%) or median (range). BMI, body mass index; MES, Mayo endoscopic subscore; MMX, multi-matrix system; 5-ASA, 5-aminosalicylate. [a]Post-treatment MES of 0 or 1. [b]Post-treatment MES of ≥2 (*n* = 4) or no clinical improvement (*n* = 1). [c]Fisher's exact test and. [d]Wilcoxon signed-rank test (comparison between patients with and without endoscopic improvement). [e]Patients who underwent endoscopy within 2 weeks before initiating treatment (overall, *n* = 11; improvement, *n* = 8; no improvement, *n* = 3).

Assessment

The primary endpoint was the rate of endoscopic improvement (MES of 0 or 1) [8] with CGM. Secondary endpoints were ADRs, changes in UC disease activity (MES/Mayo score/CAI/endoscopic findings), changes in UC symptoms recorded in the symptoms diary, rate of endoscopic remission (MES of 0) [8] with CGM, and comparison of baseline characteristics between patients with and without endoscopic improvement with CGM.

Table 2. Treatment status

	Overall	Endoscopic improvement[a]	No endoscopic improvement[b]
	N = 14	*N* = 9	*N* = 5
Duration of CGM treatment, weeks	8 (2–26)	8 (8–22)[c]	12 (2–26)
Concomitant treatment			
Oral 5-ASA and sulfasalazine			
5-ASA, MMX	12 (86)	8 (89)	4 (80)
5-ASA, granules	1 (7)	1 (11)	0 (0)
Sulfasalazine	1 (7)	0 (0)	1 (20)
Topical treatment			
None	9 (64)	6 (67)	3 (60)
5-ASA, suppositories	2 (14)	2 (22)	0 (0)
5-ASA, enemas	2 (14)	1 (11)	1 (20)
Corticosteroids, enemas	0 (0)	0 (0)	0 (0)
Immunosuppressants			
None	14 (100)	9 (100)	5 (100)
Maintenance treatment after endoscopic improvement with CGM			
Oral 5-ASA and sulfasalazine			
5-ASA, MMX	–	7 (78)	–
5-ASA, granules	–	1 (11)	–
Sulfasalazine	–	1 (11)	–
Topical treatment			
None	–	6 (67)	–
5-ASA, suppositories	–	2 (22)	–
5-ASA, enemas	–	0 (0)	–
Corticosteroids, enemas[d]	–	2 (22)	–
Remission induction treatment after discontinuing CGM			
Prednisolone	–	–	1 (20)[e]
Upadacitinib	–	–	1 (20)[e]
Ustekinumab	–	–	1 (20)[e]
Vedolizumab	–	–	1 (20)[e]
Corticosteroids, enemas	–	–	1 (20)[e]

Values are given as median (range) or *n* (%). CGM, carotegrast methyl; MMX, multi-matrix system; 5-ASA, 5-aminosalicylate. [a]Post-treatment MES of 0 or 1. [b]Post-treatment MES of ≥2 (*n* = 4) or no clinical improvement (*n* = 1). [c]8 weeks (*n* = 7), 12 weeks (*n* = 1), and 22 weeks (*n* = 1). [d]Short-term treatment (14 days). [e]Resulting in endoscopic improvement.

Statistical Analysis

We used SAS release 9.4 for Windows (SAS Institute Inc., Cary, NC, USA), Microsoft Office 365 Apps for Enterprise (Microsoft Corp., Redmond, WA, USA), and R 3.6.0 (www.r-project.org), for statistical analyses. We calculated summary statistics for patient baseline characteristics and other data collected during the study. Missing data were not imputed. The Wilcoxon signed-rank test was used to compare pre- and post-treatment MES/Mayo score/CAI. We created line graphs of the median stool and diarrhea frequencies and the percentage of patients with bloody stool and abdominal pain. The Wilcoxon signed-rank test was used to compare the stool and diarrhea frequencies on day 1 and day X, and the McNemar test was used to compare the percentage of patients with bloody stool and abdominal pain on day 1 and day X. For patients who achieved endoscopic improvement with CGM treatment, Kaplan-Meier analysis was used to plot the Kaplan-Meier curve on the basis of the time from endoscopic improvement to relapse and to calculate the cumulative relapse-free rate and its 95% confidence interval (CI) at week 26. The Wilcoxon signed-rank test (for continuous data) and Fisher's exact test (for categorical data) were used to compare baseline characteristics between patients with and without endoscopic improvement. Two-tailed $p < 0.05$ was considered statistically significant.

Results

Patient Baseline Characteristics

Fourteen patients with moderately active UC (new onset, *n* = 1; relapse, *n* = 13) were included in this study (Table 1): 71% (10/14) were women, the median

Table 3. Changes in UC disease activity

	Overall		
	N = 14		
	Pre	Post	*p* value[b]
	n = 11[a]	*n* = 13	
MES	3.0 (2–3)	0.0 (0–3)	0.008[c]
0	0 (0)	8 (62)[d,e]	
1	0 (0)	1 (8)[d]	
2	4 (36)	2 (15)	
3	7 (64)	2 (15)	
Mayo score	7.0 (5–9)	0.0 (0–9)	0.006[f]
	Pre	Post	*p* value
	n = 14	*n* = 12	
Clinical activity index	6.0 (1–11)	0.0 (0–9)	0.015[g]

Values are given as median (range) or *n* (%). MES, Mayo endoscopic subscore. [a]Patients who underwent endoscopy within 2 weeks before initiating treatment (improvement, *n* = 8; no improvement, *n* = 3). [b]Wilcoxon signed-rank test. [c]Patients with both pre- and post-treatment data (*n* = 10). [d]The rate of endoscopic improvement (MES of 0 or 1) was 64% (9/14). [e]The rate of endoscopic remission (MES of 0) was 57% (8/14). [f]Patients with both pre- and post-treatment data (*n* = 10). [g]Patients with both pre- and post-treatment data (*n* = 12).

(range) age was 47 (20–68) years, none had a smoking history, and 50% (7/14) had a disease duration of ≥5 years. UC types were proctitis in 7% (1/14), left-sided colitis in 50% (7/14), and total colitis in 43% (6/14). Recently used oral agents were 5-ASA (multi-matrix system [MMX]) in 86% (12/14), 5-ASA (granules) in 7% (1/14), and sulfasalazine in 7% (1/14). Topical agents were used concomitantly in 36% (5/14), and immunosuppressants (azathioprine) in 14% (2/14). Oral corticosteroids (prednisolone) were used previously in 14% (2/14). The baseline median (range) CAI was 6.0 (1–11). Eleven patients underwent endoscopic assessment within 2 weeks before starting CGM treatment: their baseline MES was 2 in 36% (4/11) and 3 in 64% (7/11), and their baseline median (range) Mayo score was 7.0 (5–9). Three patients underwent endoscopic assessment more than 2 weeks before starting CGM treatment. For all 3 patients, their last MES before starting CGM was 2, and their last Mayo score before starting CGM was 4, 7, and 8, respectively.

Effectiveness of CGM Treatment

The median (range) duration of CGM treatment was 8 (2–26) weeks for all 14 patients, 8 (8–22) weeks for 9 patients with endoscopic improvement, and 12 (2–26) weeks for 5 patients without endoscopic improvement (Table 2). Azathioprine and corticosteroid enemas were discontinued at the initiation of CGM, and oral and topical 5-ASA were continued concomitantly.

The rate of endoscopic improvement was 64% (9/14), and the rate of endoscopic remission was 57% (8/14) (Table 3). Pre- and post-treatment endoscopic findings are shown for 2 patients with endoscopic improvement (Fig. 1a, b) and for 1 patient without endoscopic improvement (Fig. 1c). There was no significant difference in baseline characteristics between patients with and without endoscopic improvement (Table 1).

The median (range) MES was 3.0 (2–3) before CGM treatment and 0.0 (0–3) after treatment, with a significant decrease ($p = 0.008$) in 10 patients with both pre- and post-treatment data (Table 3; Fig. 2a). The median (range) Mayo score was 7.0 (5–9) before CGM treatment and 0.0 (0–9) after treatment, with a significant decrease ($p = 0.006$) in 10 patients with both pre- and post-treatment data (Table 3; Fig. 2b). The median (range) CAI was 6.0 (1–11) before CGM treatment and 0.0 (0–9) after treatment, with a significant decrease ($p = 0.015$) in 12 patients with both pre- and post-treatment data (Table 3; Fig. 2c). Stool and diarrhea frequencies decreased significantly after initiating CGM treatment (Fig. 3a), and the percentage of patients with bloody stool and abdominal pain tended to decrease (Fig. 3b).

Patients Who Achieved Endoscopic Improvement with CGM

The cumulative relapse-free rate at week 26 among 9 patients who achieved endoscopic improvement with CGM was 77.8% (95% CI, 36.5%–93.9%) (Fig. 4). The same agents were used as maintenance treatment in 8 patients: 5-ASA as MMX in 7 and 5-ASA as granules in 1 (Table 2). Treatment was changed to sulfasalazine in 1 patient with possible intolerance to 5-ASA (MMX). Topical agents were used concomitantly in 3 patients, which comprised 5-ASA suppositories (*n* = 1), short-term (14 days) budesonide enemas (*n* = 1), and 5-ASA suppositories combined with short-term (14 days) budesonide enemas (*n* = 1).

With a median (range) follow-up duration of 358 (192–417) days after discontinuing CGM treatment, 2 patients experienced relapse (Table 4). Case 1, a 50-year-old man with left-sided colitis, experienced a relapse 82 days after the first endoscopic improvement, achieved a second endoscopic improvement with another course of CGM treatment, experienced another relapse 163 days after the

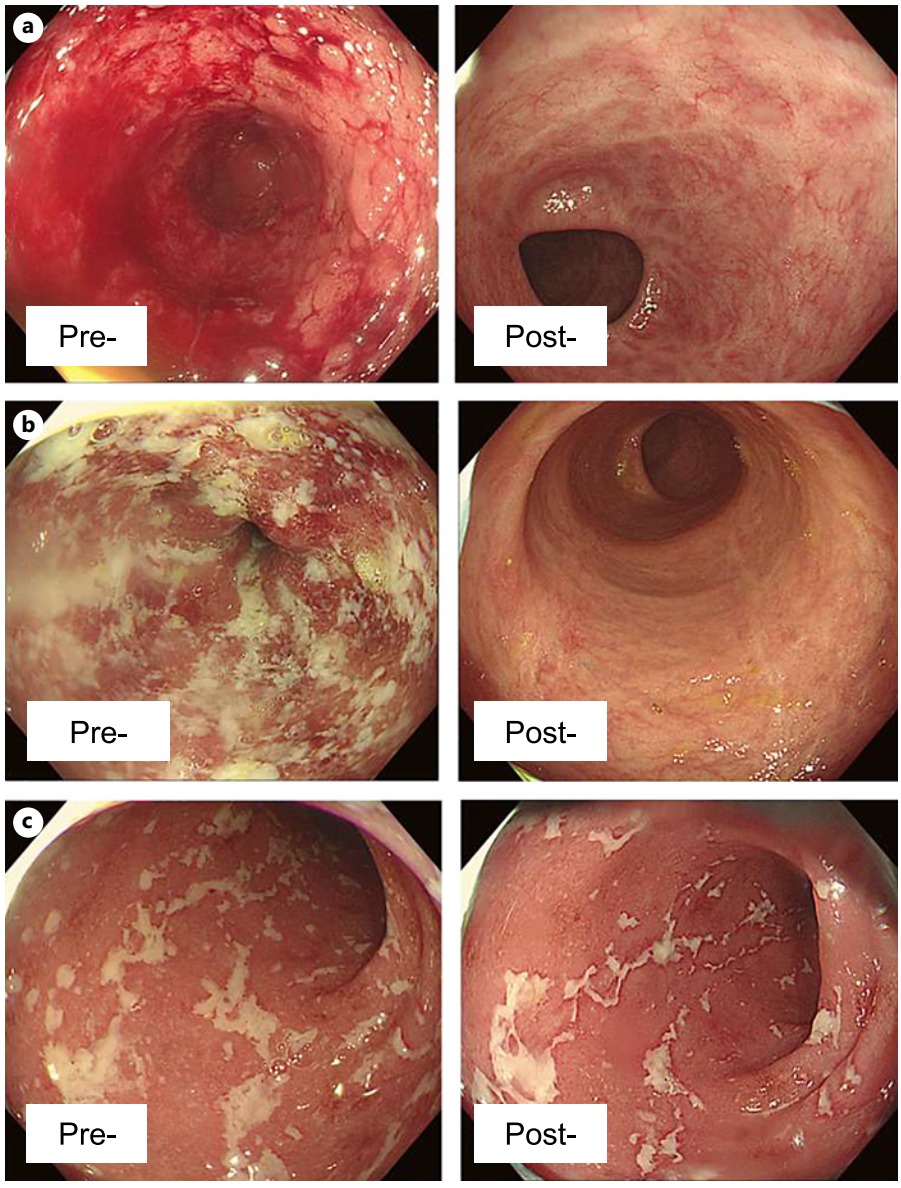


Fig. 1. Endoscopic findings. Endoscopic findings pre- and post-treatment with CGM in 2 responders (**a**, **b**) and a non-responder (**c**). **a** A 66-year-old woman with total colitis, BMI of 21.5 kg/m^2, and disease duration of 1 year. Pre-treatment: MES, 3; Mayo score, 8; clinical activity index, 6; post-treatment: MES, 0; Mayo score, 0; clinical activity index, 0. **b** A 67-year-old man with total colitis, BMI of 25.5 kg/m^2, and disease duration of 17 years. Pre-treatment: MES, 3; Mayo score, 7; clinical activity index, 4; post-treatment: MES, 0; Mayo score, 0; clinical activity index, 0. **c** A 48-year-old man with left-sided colitis, BMI of 25.0 kg/m^2, and disease duration of 9 years. Pre-treatment: MES, 3; Mayo score, 7; clinical activity index, 1; post-treatment: MES, 3; Mayo score, 6; clinical activity index, 3. BMI, body mass index; CGM, carotegrast methyl; MES, Mayo endoscopic subscore.

second endoscopic improvement, and achieved a third endoscopic improvement with filgotinib. Case 2, a 57-year-old woman with left-sided colitis, experienced a relapse 105 days after the first endoscopic improvement and achieved a second endoscopic improvement with filgotinib.

Patients Who Did Not Achieve Endoscopic Improvement with CGM

Five patients who did not achieve endoscopic improvement with CGM achieved endoscopic improvement subsequently with prednisolone (n = 1), upadacitinib (n = 1), ustekinumab (n = 1), vedolizumab (n = 1), and budesonide enemas (n = 1) (Table 2).

Safety of CGM Treatment

No ADRs were reported during the entire study period in any patient, including Case 1 (Table 4), who received another course of CGM treatment after a relapse.

Discussion

In this single-center, retrospective, observational study of Japanese patients with moderately active UC who had an inadequate response to 5-ASA, 64% (9/14) of the patients achieved the primary endpoint of endoscopic improvement. CGM treatment resulted in a significant

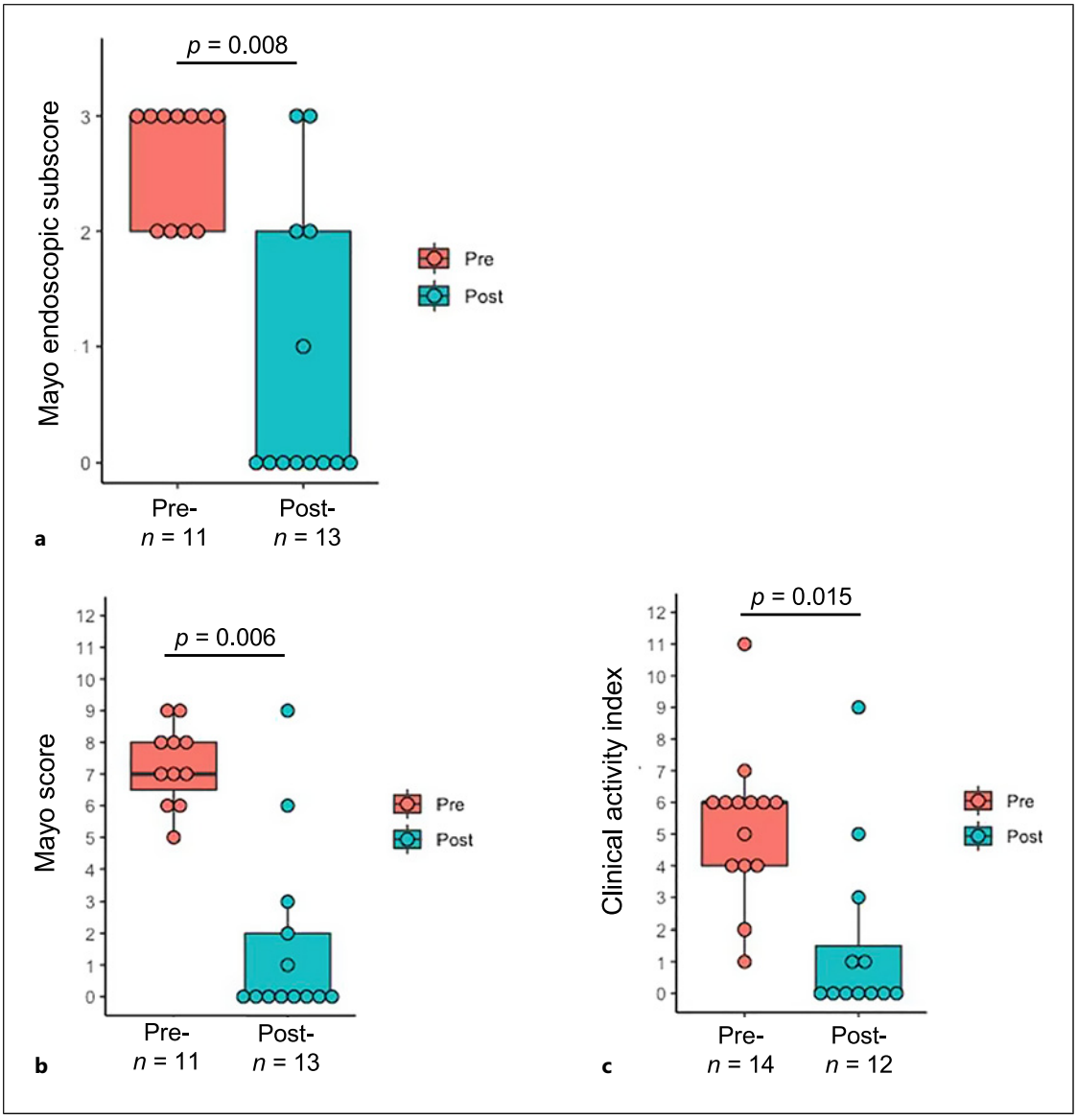
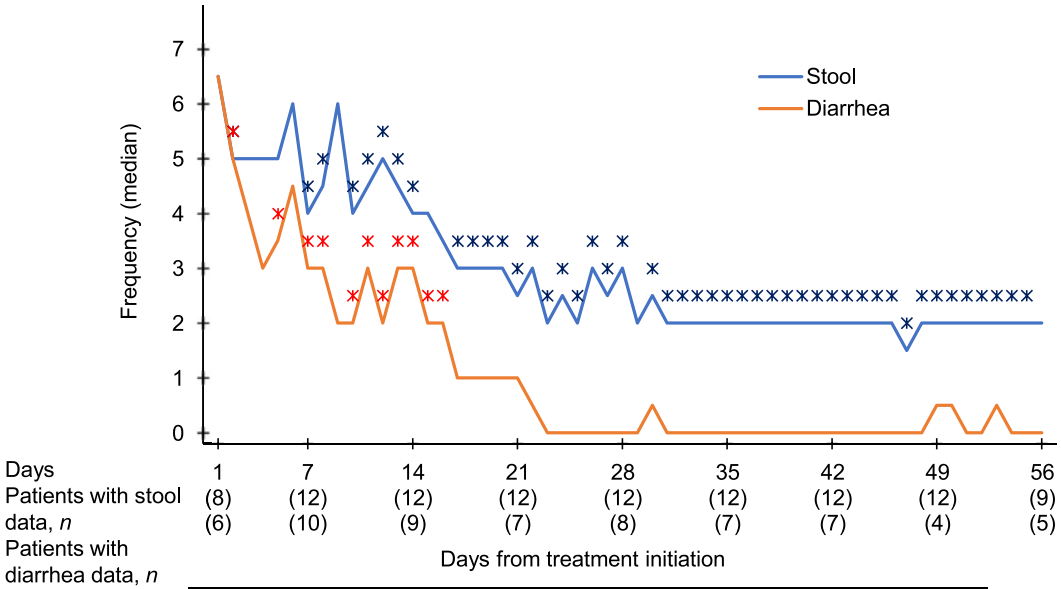


Fig. 2. Changes in UC disease activity pre- and post-treatment with CGM. Changes from before to after treatment in MES (**a**), Mayo score (**b**), and clinical activity index (**c**). Pre-treatment values appear in orange, and post-treatment values appear in green. The upper and lower edges of the box represent the upper and lower quartile values, respectively. The line that divides the box represents the median. Single points on the diagram indicate the outliers. The ends of the upper and lower whiskers represent the highest and lowest values, excluding outliers. The *p* values were calculated in patients with both pre- and post-treatment data (**a**, *n* = 10; **b**, *n* = 10; **c**, *n* = 12). CGM, carotegrast methyl; MES, Mayo endoscopic subscore; UC, ulcerative colitis.

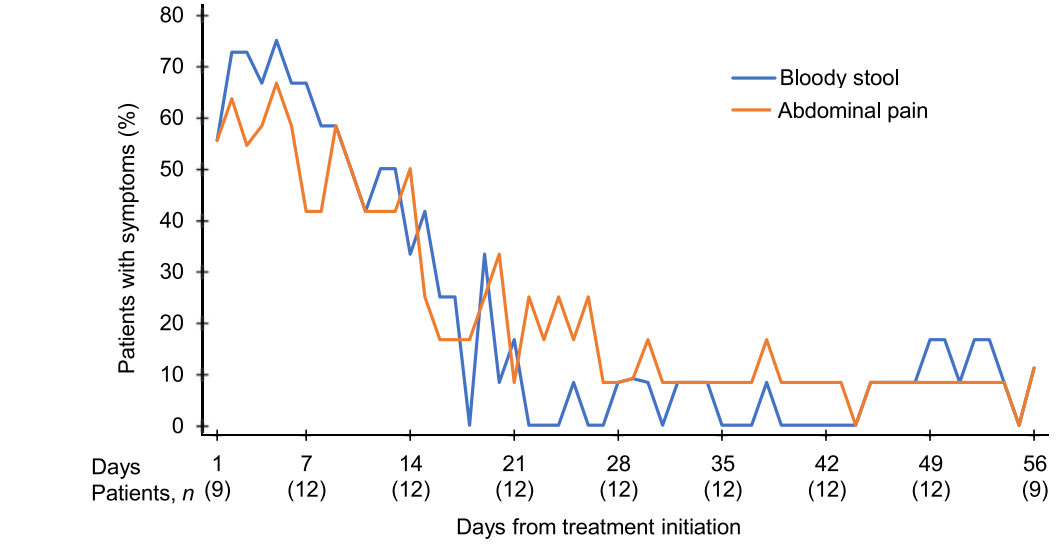
decrease in UC disease activity (MES, Mayo score, and CAI) and stool and diarrhea frequencies. No ADRs, including PML, were reported during the entire study period.

In a phase 3 study of CGM, patients were randomly assigned to receive either CGM or placebo, and the primary endpoint was the proportion of patients with a clinical response at week 8 [8]. CGM or placebo was continued until week 24 if endoscopic remission was not achieved [8]. In the present study, we retrospectively collected information on effectiveness and safety endpoints for all patients treated with CGM and followed-up every 2 weeks at our clinic. Although a direct comparison cannot be made between the phase 3 study and the present study, the rate of endoscopic improvement with CGM was 64% (9/14), with a median treatment duration



Day	1	7	14	28	56
Stool (median)	6.5	4.0	4.0	3.0	2.0
p-value (vs. Day 1)	-	0.047	0.031	0.047	0.125
Diarrhea (median)	6.5	3.0	3.0	0.0	0.0
p-value (vs. Day 1)	-	0.031	0.031	0.125	0.250

a



Day	1	7	14	28	56
Bloody stool (%)	55.6	66.7	33.3	8.3	11.1
p-value (vs. Day 1)	-	1.000	0.625	0.125	0.250
Abdominal pain (%)	55.6	41.7	50.0	8.3	11.1
p-value (vs. Day 1)	-	0.500	1.000	0.125	0.125

b

3

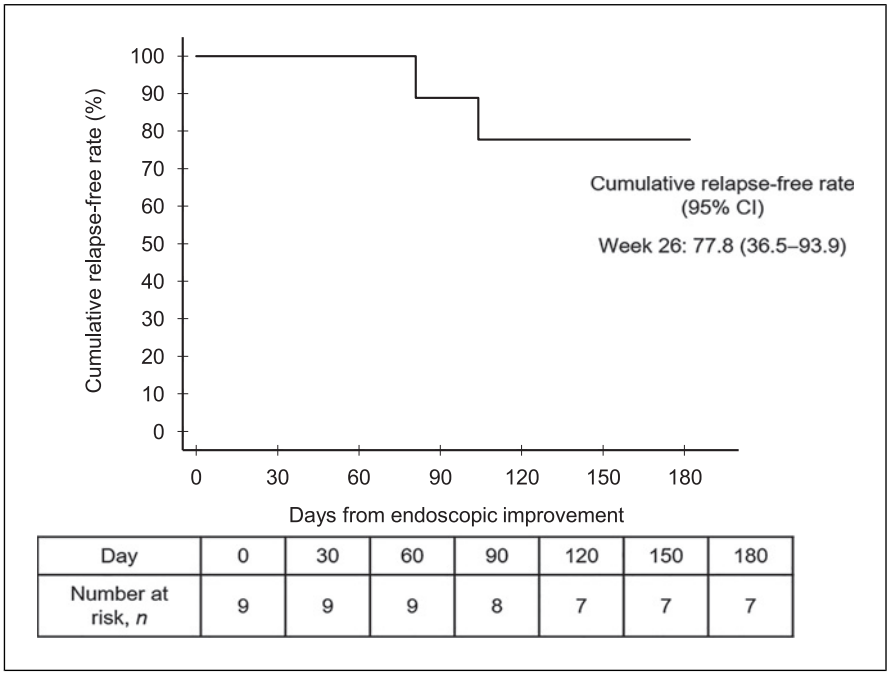
(For legend see next page.)

of 8 weeks, which was comparable to 55% (56/102) at week 8 (double-blind treatment period) and week 24 (extension treatment period) in the previous phase 3 study [8]. The rate of endoscopic remission in this study was 57% (8/14), which was numerically higher than the rates of 14% (14/102) at week 8 and 16% (16/102) at week 24 in the phase 3 study [8]. The higher endoscopic remission rate in the present study might be owing to the baseline lower disease activity: 45% (5/11) of the patients in the present study had a Mayo score of ≥8 (8 or 9), while 58% (59/102) of the patients in the phase 3 study had a Mayo score ≥8 (8–10) [8].

According to the symptoms diaries, many patients in the present study experienced symptom improvement after 1 week of CGM treatment, and most patients achieved symptom relief by week 4. In a phase 3 study of another integrin antagonist, vedolizumab (a monoclonal antibody to α4β7 integrin), there was greater improvement in Mayo subscores for stool frequency and rectal bleeding in weeks 6 and 10 compared with week 2 [14]. Considering these clinical courses of patients treated with integrin antagonists, we suggest continuing CGM for at least 4 weeks, even in patients whose symptoms improve within 2 weeks, and performing endoscopic assessment between weeks 8 and 12 to determine whether to continue CGM.

No ADRs were reported in the present study. This includes PML, which occurred in patients treated with natalizumab (a monoclonal antibody to α4-integrin), with an incidence of 2.1 cases per 1,000 patients [15]. The CGM package insert states that, to reduce the risk of PML, the maximum treatment duration of CGM should be 6 months, and that CGM should be discontinued when patients achieve remission before 6 months [16].

Because of the potential PML risk, CGM is currently used only as remission induction treatment, not as maintenance treatment. Nine patients who achieved endoscopic improvement in the present study received maintenance treatment with previous agents, such as 5-ASA. The cumulative relapse-free rate was 77.8% (95% CI, 36.5%–93.9%) at week 26, with 2 relapsed cases. Case 1 developed 5-ASA (MMX) intolerance, with a positive drug-induced lymphocyte stimulation test result. Maintenance treatment with sulfasalazine may have triggered relapse in this patient. In Case 2, CGM was discontinued early, with an MES of 1; however, continued therapy until endoscopic remission



Day	0	30	60	90	120	150	180
Number at risk, *n*	9	9	9	8	7	7	7

Fig. 4. Cumulative relapse-free rate among 9 patients who achieved endoscopic improvement with CGM treatment.

Fig. 3. Changes in UC symptoms pre- and post-treatment with CGM. Changes in the median stool (**a**, blue line) and diarrhea (**a**, orange line) frequencies and the percentage of patients with bloody stool (**b**, blue line) and abdominal pain (**b**, orange line) are shown. The *p* values were calculated using the Wilcoxon signed-rank test (**a**) or the McNemar test (**b**), comparing data on day 1 and day X. Asterisks indicate *p* values of <0.05. CGM, carotegrast methyl; UC, ulcerative colitis.

Table 4. Cases with a relapse after achieving endoscopic improvement with CGM

	Case 1	Case 2
Sex	Male	Female
Age, years	50	57
Disease duration, years	31	4
Disease status at baseline	Relapse	Relapse
UC type	Left-sided colitis	Left-sided colitis
Recent treatment	5-ASA (MMX)	5-ASA (granules) and azathioprine
MES		
Pre	–	3
Post	0	1
Mayo score		
Pre	–	9
Post	0	1
Clinical activity index		
Pre	6	6
Post	0	–
Maintenance treatment	Sulfasalazine	5-ASA (granules)
First relapse		
Duration of CGM treatment, weeks	8	8
Time from endoscopic improvement to relapse, days	82	105
Subsequent remission induction treatment	CGM	Filgotinib[a]
Second relapse		
Time from endoscopic improvement to relapse, days	163	–
Subsequent remission induction treatment	Filgotinib[a]	–

CGM, carotegrast methyl; MES, Mayo endoscopic subscore; MMX, multi-matrix system; UC, ulcerative colitis; 5-ASA, 5-aminosalicylate.
[a]Resulting in endoscopic improvement.

(MES of 0) may have been necessary. Maintenance treatment without previous azathioprine may also have contributed to relapse in this patient. Further studies are needed to determine when to discontinue CGM treatment and what agents to use as maintenance treatment to prevent relapse after discontinuing CGM. Additionally, the current Japanese treatment guidelines for UC recommend both CGM and oral prednisolone for patients with moderately active UC and an inadequate response to 5-ASA [9]. Further studies are needed to determine when to prioritize CGM over prednisolone.

All 5 patients who did not achieve endoscopic improvement with CGM achieved endoscopic improvement with subsequent remission induction treatment. One patient who achieved endoscopic improvement with vedolizumab injection experienced abdominal pain, which might have led to the 60% adherence rate and insufficient effectiveness of oral CGM. Non-adherence to IBD treatment is associated with adverse clinical outcomes, such as an increase in disease activity, relapse, and loss of response [17]. In a study investigating medication adherence among patients with IBD using the Morisky Medication Adherence Scale, medication adherence was poor among those taking oral medication instead of injections, those taking medication at a higher frequency, and those with lower understanding of the disease [18]. Treatment with CGM requires that patients take 8 tablets 3 times a day (24 tablets per day), which may lead to poor medication adherence in real-world settings. However, in the present study, all patients except the patient described above completed the daily oral intake. The relatively high adherence rate in the present study may be owing to effective patient education by the treating physician before CGM treatment was started: all patients were fully informed that CGM was a small-molecule drug that should be taken 3 times a day for the best effectiveness. Additionally, patients were informed that the majority of the drug costs (200 Japanese Yen per tablet) would be covered by public health insurance, that the maximum treatment duration of CGM

was 6 months, and that oral prednisolone, which is associated with increased risks of adverse events and corticosteroid dependency [19–21], should be used in the event that CGM treatment failed.

The present study has 3 limitations. First, this was a retrospective, observational study of a small number of patients treated with CGM in a single clinic.

Second, some disease activity and symptoms diary data were missing, owing to the retrospective study design. We did not evaluate patients' laboratory parameters, such as fecal calprotectin, C-reactive protein, hemoglobin, and albumin, owing to the lack of data. Third, endoscopic assessment in the present study was performed by a single investigator, not by blinded evaluators, which might have led to detection bias. Further studies with a larger number of patients from multiple centers are necessary to confirm the real-world safety and effectiveness of CGM demonstrated in the present study.

In conclusion, this single-center, retrospective, observational study of 14 Japanese patients with UC showed that CGM was safe and effective as remission induction treatment in patients with moderately active UC who had an inadequate response to 5-ASA in real-world settings.

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Statement of Ethics

This study was approved by the Institutional Review Board of Kanazawabunko Hospital and registered in the UMIN clinical trial registration system (UMIN000052186). All patients provided written consent, oral consent, or opt-out consent. We have obtained written informed consent from the relevant patients for the publication of identifying details and any accompanying images. Oral or opt-out consent was obtained from the patients whose identifying details or any accompanying images were not included. Oral consent and opt-out consent procedures were reviewed and approved by the Institutional Review Board of Kanazawabunko Hospital, reviewed protocol number EK-05, date of decision 7 September 2023.

Conflict of Interest Statement

Toshihide Ohmori has received honoraria from EA Pharma Co., Ltd., Kissei Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, Janssen Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation, KYORIN Pharmaceutical Co., Ltd., Daiichi Sankyo Company Limited, AstraZeneca, and Tsumura & Co., and research grants from EA Pharma Co., Ltd.

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Author Contributions

Toshihide Ohmori contributed to the conceptualization of the study, data curation, and writing, reviewing, and editing of the manuscript.

Data Availability Statement

The data generated or analyzed during this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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