ORIGINAL ARTICLE

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2025.00046
Intest Res, Published online July 14, 2025

Efficacy and safety of carotegrast methyl in active ulcerative colitis: a real-world prospective cohort study

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Background/Aims: Carotegrast methyl, an oral α4-integrin inhibitor, was recently approved for the treatment of active ulcerative colitis (UC). However, real-world data regarding its efficacy and safety remain scarce. This study aimed to assess the clinical effectiveness and safety profile of carotegrast methyl in patients with active UC. **Methods:** Patients with active UC received carotegrast methyl at a dosage of 960 mg three times daily. Treatment was discontinued at 8 weeks for patients who achieved endoscopic remission. For those not achieving endoscopic remission, treatment was continued for up to 24 weeks. Clinical and endoscopic assessments were performed at 8 and 24 weeks to evaluate treatment progress. **Results:** Among 50 UC patients, 45% achieved clinical remission, and 22% achieved endoscopic remission by week 8. Of those who discontinued treatment after reaching endoscopic remission, 55% experienced relapse during a median follow-up period of 30 weeks. For patients who continued treatment through 24 weeks, 52% achieved clinical remission, with a cumulative remission maintenance rate of 74.2%. Mild adverse events were reported in 6% of patients, including hyperamylasemia, hepatic dysfunction, and elevated biliary enzymes, all of which resolved after discontinuation of treatment. In 8 patients who relapsed and were re-administered carotegrast methyl, 62.5% achieved clinical remission, demonstrating the drug's effectiveness and safety in re-treatment. **Conclusions:** Carotegrast methyl effectively induces both clinical and endoscopic remission in patients with active UC and has a favorable safety profile. Re-administration is safe and effective for patients experiencing relapse. **(Intest Res, Published online)**

Key Words: Ulcerative colitis; Carotegrast methyl; Integrin inhibitors; Anti-inflammatory agents; Observational study

INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing-remitting inflammatory bowel disease of unknown etiology, primarily characterized by mucosal inflammation.[1,2] In recent years, the incidence of UC has been rising both domestically and internationally, prompting advances in understanding its pathophysiology and developing novel therapeutic strategies.[3,4] Conventional treatment options, centered on 5-aminosalicylic acid (5-ASA) agents and corticosteroids, have been significantly expanded with the advent of biologics, Janus kinase (JAK) inhibitors, and sphingosine-1-phosphate receptor modulators.

Received March 21, 2025. **Revised** April 30, 2025. **Accepted** May 8, 2025.
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Carotegrast methyl is an orally administered, selective α4-integrin antagonist developed in Japan as a novel therapeutic agent for inducing remission in UC.[5,6] Approved for insurance coverage in Japan in 2022, its use in clinical practice is gradually increasing.[7] The drug inhibits the binding of adhesion molecules on vascular endothelial cells (VCAM-1 and MadCAM-1) to α4β1 and α4β7 integrins, respectively, on lymphocytes.[8] This reduces lymphocyte infiltration into the colonic mucosa and exerts anti-inflammatory effects. Carotegrast methyl is recommended as an early therapeutic option, prior to steroids (prednisolone), for patients with inadequate response to or intolerance of 5-ASA, with promising evidence supporting its utility.[6,7,9]

Natalizumab, another integrin antagonist used for the treatment of multiple sclerosis, has been associated with the occurrence of progressive multifocal leukoencephalopathy (PML),

raising significant safety concerns.[10] Given these concerns, potential PML risk has also been considered for carotegrast methyl, leading to its use being restricted to a maximum treatment duration of 6 months to mitigate this risk.[11] Consequently, the drug is positioned exclusively as a remission-induction therapy in UC management.[11] In clinical trials of carotegrast methyl, a protocol was adopted in which treatment was terminated at 8 weeks if endoscopic remission was achieved.[6,7,9] If endoscopic remission was not achieved, treatment was continued until the disappearance of bloody stool or endoscopic remission was confirmed through a follow-up endoscopic examination. To further minimize the risk of PML, treatment duration was capped at 24 weeks. Notably, carotegrast methyl can be reinitiated even after treatment discontinuation, provided more than 8 weeks have elapsed since the last dose.[11]

The efficacy and safety of carotegrast methyl have been demonstrated in a large-scale domestic clinical trial.[6] However, reports on its therapeutic outcomes in real-world settings remain scarce. A recently published retrospective study, although limited in scope with only 14 patients, suggested that carotegrast methyl is both safe and effective for remission induction in patients with moderately active UC who had an inadequate response to 5-ASA in real-world settings.[7] Nevertheless, the real-world efficacy and safety of this drug have not been fully validated, and the optimal treatment approach, including the ideal duration of administration, remains unclear. Given our institution's extensive experience with carotegrast methyl in clinical practice, we conducted this study to evaluate its real-world efficacy and safety based on clinical data. Furthermore, we aimed to explore optimal administration strategies to maximize its therapeutic potential. Additionally, we monitored the clinical course following the initial treatment with carotegrast methyl, examining relapse rates and assessing the safety and efficacy of re-treatment or subsequent treatments.

METHODS

1. Patient Selection Criteria

This study was a prospective cohort study conducted at the Yokkaichi Hazu Medical Center. The eligibility criteria for carotegrast methyl treatment at our institution were as follows: (1) patients diagnosed with UC based on endoscopic and histological findings; (2) patients with clinically and endoscopically moderate UC who were eligible for outpatient treatment (however, patients in clinical remission or with mild clinical activity but endoscopically moderate UC were also considered eligible as an exception); (3) patients who exhibited an inadequate response to or intolerance of 5-ASA formulations (including topical agents) or budesonide formulations (including topical agents); (4) patients who provided informed consent for endoscopic examinations at the start of treatment and during the treatment period; and (5) patients who agreed to blood sampling and fecal biomarker tests. Exclusion criteria included: (1) patients with severe disease on endoscopy (presumed ineffective due to the drug's characteristics); (2) patients currently using biologics, JAK inhibitors, thiopurines, or calcineurin inhibitors (tacrolimus or cyclosporine); (3) patients with a history of malignancy; (4) patients with severe hepatic dysfunction; (5) pregnant women or those planning pregnancy; and (6) patients with acute severe conditions, such as toxic megacolon, sepsis, peritonitis, or infectious colitis.

2. Carotegrast Methyl Treatment

The JC virus (John Cunningham virus) serology test was not performed before starting treatment with carotegrast methyl. Carotegrast methyl was administered orally at a dose of 960 mg (8 tablets of CAROGRA Tablets 120 mg; EA Pharma Co., Ltd., Tokyo, Japan) three times daily after meals.[11] After initiating treatment, patients visited the clinic at 2- or 4-week intervals for clinical symptom evaluations, as well as blood and stool tests. During the first year after the drug's release, only a 2-week prescription was permitted. Therefore, patients were required to visit the clinic every 2 weeks. Treatment was discontinued in cases of inefficacy, clinical deterioration, or adverse events, based on the attending physician's judgment, and alternative treatments, including corticosteroids, were initiated. As per the large domestic trial protocol,[6] endoscopic evaluation was performed at week 8 for patients receiving carotegrast methyl. For cases achieving endoscopic remission, treatment was terminated. If endoscopic remission was not achieved, treatment was continued until bloody stools disappeared or endoscopic remission was confirmed through a follow-up endoscopic examination, for up to a maximum of 24 weeks. In this study, treatment could be extended to 24 weeks at the discretion of the attending physician if deemed beneficial. The maximum duration of carotegrast methyl treatment was set at 24 weeks for all cases. In cases where improvement was observed with carotegrast methyl, prednisone was tapered and, if possible, discontinued. However, the dose of mesalazine was not altered and continued at the same dosage.

3. Assessment of Treatment Efficacy

Clinical disease activity was assessed at 2- or 4-week intervals using the sum of the Mayo score's stool frequency subscore (0–3) and rectal bleeding subscore (0–3), with a total score ranging from 0 to 6.[12] Remission was defined as a total score of 0, mild disease as 1–2, moderate disease as 3–4, and severe disease as 5–6. Clinical remission was defined as a total score of 0, while improvement was defined as a decrease of at least 1 point in the total score.

Endoscopic evaluation was performed for all cases at the start of treatment to assess disease severity. Endoscopy was repeated at week 8 for patients continuing carotegrast methyl treatment, and as needed thereafter based on the attending physician's judgment. Endoscopic disease activity was assessed using the Mayo Endoscopic Subscore, a 4-point scale: 0 = normal or inactive disease, 1 = mild activity (erythema, decreased vascular pattern, mild friability), 2 = moderate activity (marked erythema, absent vascular pattern, friability, erosions), and 3 = severe activity (spontaneous bleeding, ulceration). Endoscopic remission was defined as a Mayo Endoscopic Subscore of 0.

Blood tests were conducted at the start of treatment, at week 8, and as needed, including the following parameters: white blood cell count, hemoglobin, platelet count, C-reactive protein, erythrocyte sedimentation rate, total protein, and albumin. Concurrently, stool samples were collected for fecal calprotectin measurement. Stool samples were obtained by patients in the early morning within 5 days before their clinic visit and stored at room temperature until submission. The samples were analyzed using a NS-Prime automatic analyzer (Alfresa Pharma Co., Ltd., Osaka, Japan).[13] Laboratory investigators were blinded to the clinical data.

4. Ethical Considerations

Before starting this study, our investigation protocol was approved by the Ethical Committee at Yokkaichi Hazu Medical Center (reference number 1124). All included patients agreed to participate in this study after being informed regarding our study purpose and the procedures used during the study. Further, all investigations in this study were conducted in accordance with the principles of the Declaration of Helsinki.

5. Statistical Analysis

Frequencies were compared using the chi-square test with Yates' correction. Median values were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test (for more than 2 groups). The cumulative remission maintenance rate was calculated using the Kaplan-Meier method. Statistical significance was set at $P<0.05$.

RESULTS

1. Patient Background

In Japan, following the insurance listing of carotegrast methyl

Table 1. Baseline Characteristics of the 50 Patients in This Study

Characteristic	No. (%)
Age at study entry (yr), median (range)	46 (16–79)
Sex	
Male	30 (60)
Female	20 (40)
Duration of UC before entry (mo), median (range)	94 (2–312)
UC disease distribution	
Pancolitis	25 (50)
Left-sided colitis	24 (48)
Proctitis	1 (2)
Medication at baseline	
Oral mesalazine	44 (88)
Topical mesalazine	16 (32)
Oral budesonide	0
Budesonide enema	4 (8)
Corticosteroids	2 (4)
Azathioprine, biologics, or JAK inhibitors	0
Medication history	
Prednisolone	27 (54)
Oral budesonide	6 (12)
Budesonide enema	28 (56)
Azathioprine	6 (12)
Biologics	1 (2)[a]
JAK inhibitor	0
Clinical disease activity	
Remission	3 (6)
Mild	24 (48)
Moderate	22 (44)
Severe	1 (2)
Endoscopic disease activity	
Moderate	50 (100)
Indication for carotegrast methyl	
Inadequate response to 5-ASA	45 (90)
Intolerance to 5-ASA	5 (10)

[a]Vedolizumab.
UC, ulcerative colitis; JAK, Janus kinase; 5-ASA, 5-aminosalicylic acid.

in May 2022, 50 UC patients who met the eligibility criteria were included in the study. The baseline characteristics at the initiation of carotegrast methyl treatment are shown in Table 1. Among the 50 patients, 60% were male, with a median age of 46 years and a median disease duration of 94 months. Disease extension was classified as pancolitis in 50%, left-sided colitis in 48%, and proctitis in 2%. While clinical activity showed cases of remission or mild disease, all patients had moderate disease in terms of endoscopic activity, indicating the need for treatment. The reason for introducing carotegrast methyl was 5-ASA non-response in 45 patients (90%) and 5-ASA intolerance in 5 patients (10%). Before starting carotegrast methyl, the dose of 5-ASA was maximized in all cases. Regarding medication history, 27 patients (54%) had a history of steroid use, 6 patients (12%) had a history of immunomodulators, and 1 patient (2%) had used vedolizumab. No patients had a history of JAK inhibitor treatment. At the time of treatment initiation, 2 patients (4%) were on oral prednisolone, and 4 patients (8%) were receiving budesonide enema therapy, but no patients were receiving immunomodulators or biologics.

2. Treatment Outcomes

1) Results at 8 Weeks

The treatment course of 50 patients who received carotegrast

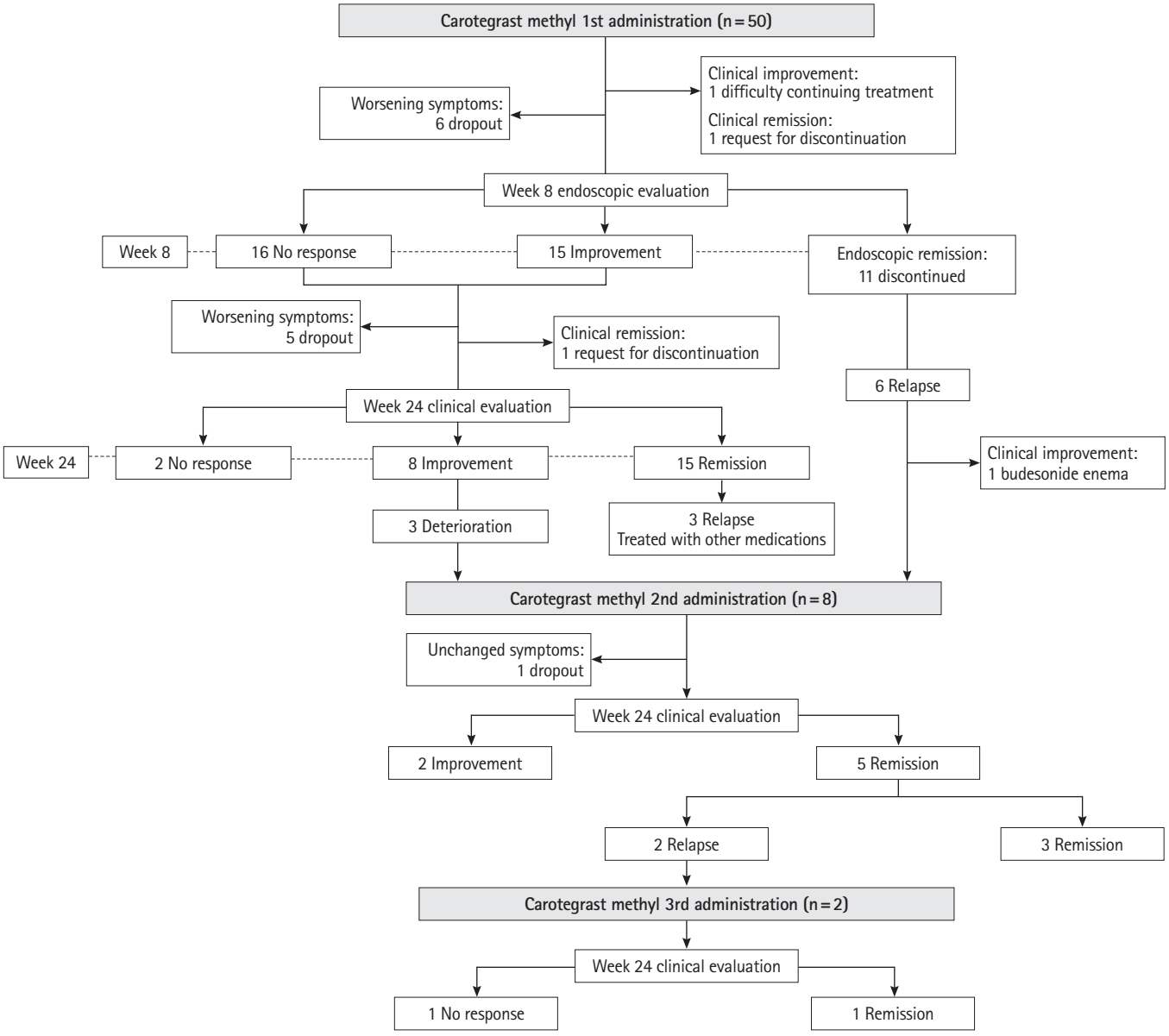

Fig. 1. The treatment course of 50 patients receiving carotegrast methyl therapy is summarized.

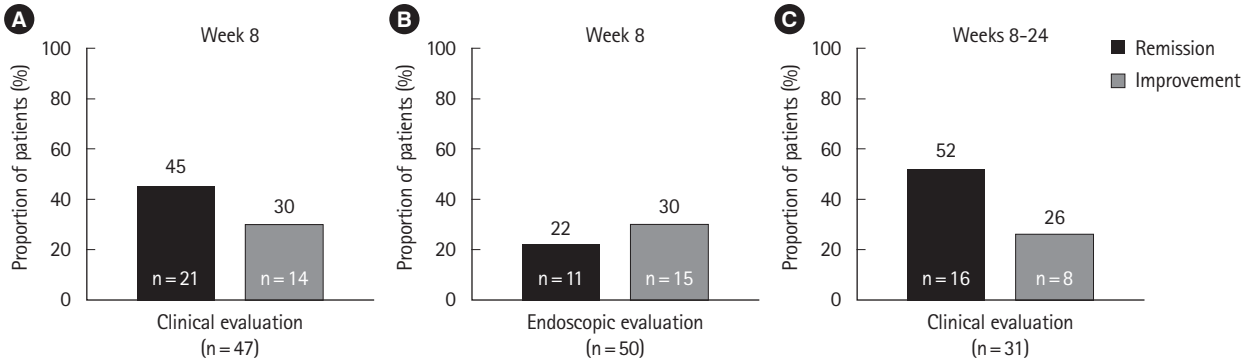

Fig. 2. Clinical and endoscopic response. (A) Among the 47 patients who had clinical disease activity at the start of treatment, the clinical efficacy at 8 weeks was 45% remission, 30% improvement, and 25% non-response. (B) The endoscopic efficacy at week 8 was remission in 11 patients (22%), improvement in 15 (30%), and no response in 24 (48%). Patients who discontinued treatment by week 8 were counted as having no response. (C) Clinical outcomes for the 31 patients from 8 weeks to 24 weeks were as follows: remission in 16 patients (52%), improvement in 8 (26%), and no response in 7 (22%), including 5 cases of treatment interruption due to symptom worsening.

Table 2. Relationship between Baseline Clinical Background and Endoscopic Outcomes at Week 8

Variable	Endoscopic remission (n = 11)	No endoscopic remission (n = 39)	*P*-value
Age (yr), median (range)	45 (16–55)	46 (18–79)	0.36
Male sex	7 (64)	23 (59)	0.78
Duration of UC (mo), median (range)	53 (2–269)	99 (3–312)	0.28
UC disease distribution			0.79
Pancolitis	5 (45)	20 (51)	
Left-sided colitis	6 (55)	18 (46)	
Proctitis	0	1 (3)	
Medication at baseline			
Oral mesalazine	10 (91)	34 (87)	0.74
Dose of oral mesalazine (mg/day), median (range)	4,800 (2,400–4,800)	4,400 (2,400–4,800)	0.72
Topical mesalazine	3 (27)	13 (33)	0.70
Budesonide enema	0	4 (10)	0.27
Corticosteroids	1 (9)	1 (3)	0.33
Medication history			
Prednisolone	4 (36)	23 (59)	0.47
Oral budesonide	0	6 (15)	0.17
Budesonide enema	4 (36)	24 (62)	0.14
Azathioprine	2 (18)	4 (10)	0.48
Biologics	0	1 (3)	0.59
Clinical disease activity at entry			0.28
Remission	0	3 (8)	
Mild	8 (73)	16 (41)	
Moderate	3 (27)	19 (48)	
Severe	0	1 (3)	
Indication for carotegrast methyl			0.91
Inadequate response to 5-ASA	10 (91)	35 (90)	
Intolerance to 5-ASA	1 (9)	4 (10)	

Values are presented as number (%) unless otherwise indicated.
UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid.

methyl is shown in Fig. 1. Three patients in clinical remission at study initiation were excluded from the clinical assessment. The clinical efficacy at the 8-week point for the entire group of 47 patients was as follows: remission in 21 patients (45%), improvement in 14 patients (30%), and no response in 12 patients (25%) (Fig. 2A). In particular, among the 5 patients intolerant to 5-ASA, 2 achieved clinical remission, 1 showed clinical improvement, and 2 showed no clinical response. By the 8-week point, 8 patients (16%) had discontinued treatment, while 42 patients continued. The reasons for discontinuation were as follows: 6 patients experienced worsening symptoms (leading to treatment interruption and a change of medication), 1 patient had difficulty continuing treatment due to the high number of tablets despite clinical improvement, and 1 patient discontinued based on personal preference, requesting to stop treatment after achieving clinical remission. For the 6 patients whose symptoms worsened, carotegrast methyl was discontinued, with 3 patients switching to filgotinib, 1 patient switching to filgotinib + prednisolone, and 2 patients switching to budesonide enema. In all cases, the new treatments were effective. Excluding the 8 patients who discontinued carotegrast methyl treatment, 42 patients underwent endoscopic evaluation at the 8-week point. The endoscopic results were: remission in 11 patients (22%), improvement in 15 patients (30%), and no response in 24 patients (48%) (Fig. 2B). Patients who discontinued treatment by week 8 were counted as having no response. The progression of endoscopic inflammation in 2 typical cases where carotegrast methyl was effective is shown in Supplementary Fig. 1. In these cases, improvement in bloody stools and stool frequency was observed around the third day after starting treatment, and bloody stools completely disappeared within about 1 week, with stool frequency normalizing. The endoscopic evaluation at 8 weeks confirmed remission.

Subsequently, the clinical factors significantly associated with the endoscopic efficacy of carotegrast methyl were examined. When the 11 patients who achieved endoscopic remission were compared to the 39 patients who did not, no significant differences were found in terms of age, sex, disease duration, disease extent, concomitant mesalazine treatment, past or concurrent steroid treatment, history of immunomodulator therapy, history of biologic therapy, or indication for carotegrast methyl treatment at the time of treatment initiation (Table 2). Furthermore, the relationship between the following laboratory data at the start of treatment and endoscopic efficacy was examined: white blood cell count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, hemoglobin level, platelet count, albumin level, C-reactive protein level, and fecal calprotectin level (Table 3). However, none of these indicators showed a significant relationship with endoscopic efficacy.

According to the protocol established before the trial, the 11 patients who achieved endoscopic remission discontinued carotegrast methyl treatment and were followed up. After discontinuation, maintenance therapy primarily consisted of continued mesalazine without dose adjustment, and neither thiopurines nor advanced therapies were introduced. Among patients intolerant to 5-ASA, maintenance therapy after carotegrast methyl discontinuation mainly involved careful monitoring without the use of immunosuppressants or advanced therapies, unless relapse occurred. The median follow-up period was 30 weeks (range, 1–69 weeks), during which 6 patients

Table 3. Relationship between Baseline Laboratory Values and Endoscopic Outcomes at Week 8

Variable	Endoscopic remission (n = 11)	No endoscopic remission (n = 39)	*P*-value
White blood cell count (/μL)	6,400 (4,600–11,100)	6,300 (3,900–11,100)	0.69
Neutrophil count (/μL)	3,800 (1,900–8,600)	3,700 (1,600–8,100)	0.68
Lymphocyte count (/μL)	1,600 (1,100–2,500)	1,500 (800–2,600)	0.76
Monocyte count (/μL)	500 (100–800)	500 (300–1,000)	0.26
Eosinophil count (/μL)	200 (100–600)	200 (0–700)	0.28
Hemoglobin level count (g/dL)	13.3 (11.3–15.2)	13.5 (10.4–15.8)	0.78
Platelet count ($\times 10^3$/μL)	327 (188–405)	286 (144–471)	0.49
Albumin (g/dL)	4.4 (3.9–5.5)	4.2 (3.0–4.9)	0.12
C-reactive protein (mg/dL)	0.09 (0.01–0.25)	0.15 (0.01–1.12)	0.21
Fecal calprotectin (μg/g)	1,535 (547–7,641)	1,094 (25–11,374)	0.12

Values are presented as median (range).

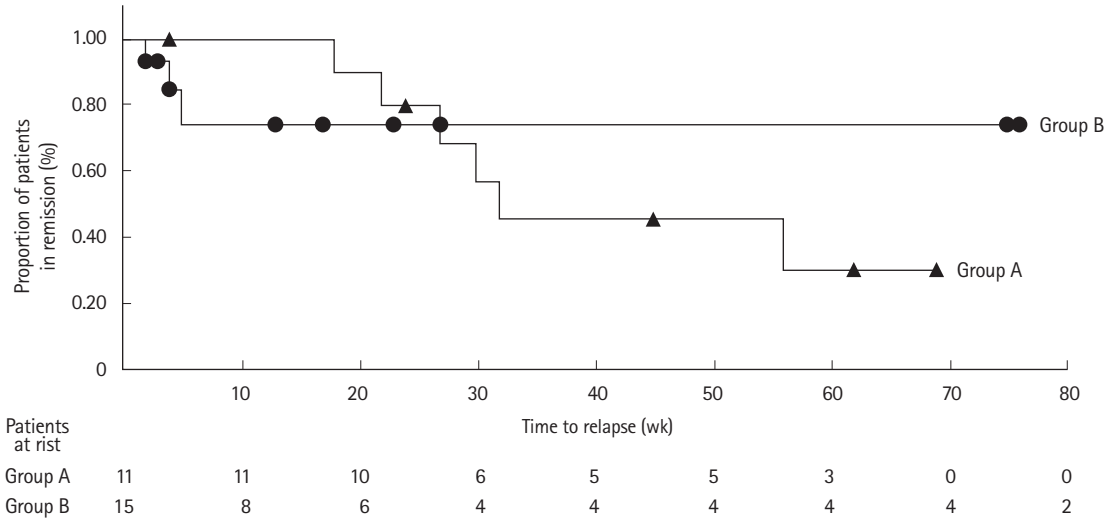

Fig. 3. The cumulative remission maintenance rates were presented for patients who achieved endoscopic remission at week 8 and discontinued carotegrast methyl (Group A), and for those who achieved clinical remission at week 24 and discontinued treatment (Group B). Due to the small sample size, no statistical comparisons were performed.

(55%) experienced relapse. The cumulative remission maintenance rate for those who achieved endoscopic remission was 30.5% (95% confidence interval [CI], 0%–63.1%), and the median time to relapse was 27 weeks (range, 18–56 weeks) (Fig. 3). Among the 6 relapsed patients, 1 was treated with budesonide enema (which resulted in remission), and 5 received re-administration of carotegrast methyl (Fig. 1). The outcomes of the 5 patients treated with re-administration of carotegrast methyl are presented later. No significant differences in clinical factors, including clinical activity at week 8, were observed between patients who relapsed and those who did not.

2) Results from 8 to 24 Weeks

For the 31 patients who did not achieve endoscopic remission at 8 weeks, carotegrast methyl treatment was continued (Fig. 1). During the carotegrast methyl treatment period up to 24 weeks, no additional advanced therapies such as corticosteroids, thiopurines, biologics, or JAK inhibitors were introduced. All patients maintained their baseline mesalazine dose without changes. Of these 31 patients, 5 discontinued treatment due to worsening symptoms, and 1 patient achieved clinical remission and chose to stop treatment based on personal preference. By the 24-week point, 25 patients had completed the treatment. The treatment outcomes for the 31 patients after 8 weeks were: clinical remission in 16 patients (52%), improvement in 8 patients (26%), and no response in 7 patients (22%, including 5 cases of treatment interruption due to symptom worsening) (Fig. 2C). The 5 patients who discontinued treatment due to worsening symptoms all switched to filgotinib, and all of them showed efficacy. Of the 8 patients who showed improvement but did not achieve remission between 8 and 24 weeks, the following additional treatments were added after discontinuation of carotegrast methyl: filgotinib in 2 patients, vedolizumab in 2 patients, mesalazine enema in 1 patient, azathioprine in 1 patient, and no additional treatment in 2 patients. All of these additional treatments were effective. In the 16 patients who achieved clinical remission, carotegrast methyl treatment was discontinued, and no additional treatments were given, with patients being followed up. Among the 15 patients who continued treatment until 24 weeks and achieved clinical remission, 3 patients (20%) experienced relapse during the median follow-up period of 5 weeks (range, 2–76 weeks). The cumulative remission maintenance rate for these 15 patients was 74.2% (95% CI, 48.3%–100.0%) (Fig. 3). The 3 relapsed patients were treated with filgotinib (n = 2) and prednisolone (n = 1), all of which were effective (Fig. 1).

3) Carotegrast Methyl Re-administration Results

In cases where the initial treatment was effective but relapse occurred after treatment discontinuation, re-administration was performed if more than 8 weeks had passed since the end of the initial treatment.[11] A total of 8 patients received re-administration, and their treatment outcomes are shown in Fig. 1. The re-administration was conducted using the same protocol as the initial treatment. Of the 8 patients, 1 was judged to be ineffective by the 18th week of re-administration and switched

to filgotinib, while the remaining 7 continued treatment until the 24th week. The final treatment outcomes were clinical remission in 5 patients (62.5%), improvement in 2 patients (25%), and no response in 1 patient (as previously described) (12.5%). Of the 5 patients who achieved remission, 2 experienced relapse again, and both received a third round of carotegrast methyl treatment. In the third treatment, both patients continued treatment until the 24th week, with 1 achieving clinical remission, while the other was ineffective endoscopically and switched to oral budesonide.

3. Adverse Events

During the initial treatment with carotegrast methyl, adverse events were observed in the following 3 cases: 1 case of hyperamylasemia (2%), 1 case of hepatic dysfunction (2%), and 1 case of elevated biliary enzymes (2%). All of these were mild laboratory abnormalities without clinical symptoms. The abnormalities promptly improved after treatment was discontinued. No adverse events were observed during re-administration or the third round of treatment with carotegrast methyl. Throughout the entire study period, no clinically significant side effects, including PML, were observed.

DISCUSSION

Real-world data on the efficacy and safety of carotegrast methyl remain scarce.[7] This prospective study evaluated treatment outcomes, focusing on the validity of an 8-week endoscopic assessment-based strategy and its appropriate use. A key strength is its prospective design, involving a relatively large single-center cohort of 50 patients, all treated and assessed using standardized protocols. Endoscopic evaluation at 8 weeks determined treatment continuation or discontinuation for those in remission and extension up to 24 weeks for others. Since mucosal healing is crucial for long-term prognosis in UC,[14,15] timely treatment decisions not only enhance outcomes but also reduce side effects and healthcare costs. Additionally, the study examined optimal treatment duration within a 24-week limit to mitigate PML risk.[11] These findings contribute to optimizing carotegrast methyl use in clinical practice and informing future treatment strategies.

In this study, among the 47 patients who had clinical disease activity at the start of treatment, the clinical efficacy at 8 weeks was 45% remission, 30% improvement, and 25% non-response, with 75% showing a response to treatment. The endoscopic assessment at 8 weeks showed 22% remission, 30% improvement, and 48% non-response, with mucosal healing confirmed in approximately 25% of cases. Due to differences in clinical evaluation criteria between studies, it is challenging to compare clinical efficacy; however, since the definition of endoscopic remission is consistent across studies, comparisons are possible. In the large domestic trial, the endoscopic remission rate at 8 weeks was 14%,[6] lower than our rate of 22%. On the other hand, recent real-world data reported a higher rate of 57%, though this study evaluated only 14 patients.[7] Thus, differences in endoscopic remission rates are observed between studies. Improvement in bloody stools and stool frequency was observed within 3 days of starting treatment, with bloody stools completely disappearing within 1 week and stool frequency normalizing. Mucosal healing was achieved in many of these cases. In patients where carotegrast methyl was particularly effective, a clear response was observed within a few days to 1 week of treatment initiation. We examined potential clinical factors associated with the efficacy of carotegrast methyl but were unable to identify any significant correlations. In particular, disease extent did not influence the drug's effectiveness. Additionally, based on the mechanism of action of this drug, we hypothesized that there might be some correlation between its efficacy and lymphocyte count; however, no significant correlation was found between laboratory data, including lymphocyte count, and its efficacy. Previous studies also failed to identify clinical factors associated with carotegrast methyl efficacy.[6,7]

The optimal administration period for carotegrast methyl remains a subject of discussion, with no definitive consensus reached to date. Vedolizumab, an anti-α4β7 monoclonal antibody, has been reported to achieve its maximum induction effect in patients with mild to moderate UC after 16 to 24 weeks of treatment.[16] Therefore, in the large domestic trial of carotegrast methyl, administration for up to 24 weeks was permitted, with the maximum cumulative effect confirmed after 12 weeks of treatment. Furthermore, the median time to complete induction therapy with carotegrast methyl was reported to be approximately 14 weeks.[6] In our study, among the 31 patients who did not achieve mucosal healing at 8 weeks and continued treatment, the clinical remission rate was 52%, the improvement rate was 26%, and the non-response rate was 22%, resulting in an overall response rate of 78% after 8 weeks. This rate was nearly equivalent to the response rate within 8 weeks. These results suggest that continuing treatment even if mucosal healing is not achieved at 8 weeks can lead to further improvement in clinical symptoms in many patients. Therefore,

continuing treatment with carotegrast methyl is considered useful even if the effect at 8 weeks is insufficient. However, if signs of clinical deterioration or worsening severity appear, switching to other treatment options should be considered.

An additional important finding of this study was observed. Among the 11 cases that achieved mucosal healing and completed treatment at 8 weeks, 55% experienced relapse during the subsequent 30-week follow-up, with the median time to relapse being 27 weeks, which was shorter than expected. The reason for the relatively high relapse rate despite achieving mucosal healing is unclear, but it is believed that detailed histological evaluation will be necessary in the future. On the other hand, in the 15 cases where treatment with carotegrast methyl was continued up to 24 weeks and clinical remission was achieved, although the follow-up period was shorter, the relapse rate was low at 20%. From the perspective of preventing relapse, extending the treatment period even in patients who achieved mucosal healing at 8 weeks without ending treatment may be an effective strategy. Currently, there is insufficient data on the optimal duration of the extension. Based on our clinical experience, we believe that attempting an extension in 4-week or 8-week intervals while monitoring clinical symptoms and fluctuations in biomarkers may be a reasonable approach, though there is no clear evidence to support this at present. Treatment discontinuation could be considered when the relapse risk is judged to be low.

There were 8 cases in which carotegrast methyl was re-administered after the initial treatment was completed. Among these, 1 case had treatment discontinued at week 18 due to lack of effectiveness, while the remaining 7 cases continued treatment until 24 weeks, with 5 achieving clinical remission and 2 showing improvement. Thus, re-administration of carotegrast methyl showed high efficacy, but in our experience, the response was somewhat weaker compared to the initial treatment, and improvement tended to take slightly longer. Of the 5 cases that achieved remission after re-administration, 2 relapsed. These 2 relapsed cases received a third dose of carotegrast methyl, with treatment continuing until 24 weeks. Of the 2, 1 achieved clinical remission, while the other did not respond, necessitating a change in treatment.

Carotegrast methyl is primarily positioned as an early induction therapy for patients with moderately active UC who exhibit an inadequate response or intolerance to 5-ASA, offering a treatment alternative before considering immunosuppressants or biologics. However, given its current limitation for long-term maintenance therapy, its clinical role must be carefully considered in comparison with other oral agents, such as JAK inhibitors and sphingosine-1-phosphate receptor modulators, which are available for both induction and maintenance phases.

The incidence of adverse events during carotegrast methyl treatment was low, with mild elevations in serum amylase, liver enzymes, and biliary enzymes observed in 2% of cases. These were minor abnormalities in laboratory values without accompanying clinical symptoms. Additionally, no adverse events were seen during re-administration or further re-dosing. These findings suggest that carotegrast methyl can be safely used repeatedly, with no increase in adverse events, similar to its initial use.[6,7] The manufacturer of the drug has adopted a policy of using carotegrast methyl only for induction of remission and discontinuing treatment after a maximum of 24 weeks, taking into account the risk of PML.[11] It is important to note that the previously concerning risk of PML has not been observed in this study or any prior trials, suggesting that the current risk appears to be very low. This approach may be 1 factor contributing to the safety of the treatment.

This study has several limitations. It is a prospective single-center study with a small sample size of 50 cases, so larger, multi-center studies are needed to confirm the findings. The absence of a control group also prevents comparison with other treatments, such as vedolizumab, an integrin antagonist. Additionally, while endoscopic assessment at 8 weeks determines treatment duration, high relapse rates after discontinuation suggest that treatment should continue even with mucosal healing. Further research is needed to determine the optimal treatment duration for carotegrast methyl and its best usage in individualized UC management.

In conclusion, carotegrast methyl is a safe and effective treatment for UC remission, though its optimal use is not yet fully established. Extending treatment beyond 8 weeks, even without mucosal healing, may lead to clinical improvement. Re-administration is safe, with no PML cases reported. Future large-scale, multi-center studies are needed, along with comparisons to other treatments and further exploration of the ideal treatment duration.

ADDITIONAL INFORMATION

Funding Source

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Data Availability Statement
Not applicable.

Author Contributions
Conceptualization: Yamamoto T. Data curation: all authors. Formal analysis: Shimoyama T, Yamamoto T. Investigation: Yamamoto T. Methodology: Shimoyama T, Yamamoto T. Project administration: Yamamoto T. Supervision: Yamamoto T. Writing - original draft: Shimoyama T. Writing - review & editing: Yamamoto T, Miyao H, Aota S, Morita S, Sakaguchi R. Approval of final manuscript: all authors.

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Supplementary Material
Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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