Cureus
Part of SPRINGER NATURE

Open Access Case Report

# Simultaneous Initiation of Carotegrast Methyl and Corticosteroids for the Induction of Remission in Moderately Active Ulcerative Colitis: Two Case Reports

Haruo Oka [1], Tsuyoshi Suda [1, 2], Miyabi Miura [1], Kiichiro Kaji [1], Kuniaki Arai [1], Shuichi Terasaki [1]

1. Gastroenterology, Japanese Red Cross Kanazawa Hospital, Kanazawa, JPN 2. Gastroenterology, Fukui Prefectural Hospital, Fukui, JPN

**Corresponding author:** Tsuyoshi Suda, t.suda1112@gmail.com

**Review began** 07/18/2026
**Review ended** 09/04/2026
**Published** 10/21/2026

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**DOI:** 10.7759/cureus.118325

## Abstract

Carotegrast methyl (CGM), an oral selective α4 integrin antagonist, has recently been approved in Japan for the induction of remission in patients with moderately active ulcerative colitis (UC). Although systemic corticosteroids remain standard therapy for remission induction, their use is limited by adverse effects, and evidence regarding the safety and efficacy of concomitantly used CGM and corticosteroids remains scarce. We report two cases of moderately active UC in which remission was successfully induced using concomitant CGM and systemic corticosteroids. In both patients, CGM was initiated together with oral prednisolone, followed by a planned steroid taper. Both patients showed prompt improvement in symptoms and inflammatory markers, with endoscopic improvement within two weeks. Steroids were successfully discontinued within four to five weeks, and sustained clinical remission was maintained without serious adverse events. These cases suggest that concomitant use of CGM and systemic corticosteroids may be a safe and effective strategy for remission induction in moderately active UC, potentially facilitating early steroid tapering. Further studies are warranted to clarify the optimal role and safety profile of this combination therapy.

**Categories:** Gastroenterology
**Keywords:** carotegrast methyl, corticosteroids, remission, remission induction, simultaneous initiation, ulcerative colitis

## Introduction

In recent years, carotegrast methyl (CGM) has been approved in Japan as a therapeutic option for the induction of remission in patients with moderately active ulcerative colitis (UC) [1]. Systemic corticosteroids have been the conventional treatment for inducing remission. Nevertheless, their long-term use is associated with a number of adverse effects, including peptic ulcer disease, hyperglycemia, psychiatric symptoms, and muscle weakness [2]. CGM is a selective α4 integrin antagonist that inhibits lymphocyte trafficking to the intestinal mucosa [3]. It has been reported to be clinically efficacious while potentially avoiding the broad immunosuppressive effects associated with systemic corticosteroids [4]. Given their distinct mechanisms of action, the simultaneous initiation of CGM and systemic corticosteroids may facilitate early remission induction and corticosteroid tapering, thereby potentially reducing the duration of corticosteroid treatment.

UC is a chronic inflammatory bowel disease characterized by a relapsing and remitting clinical course, making accurate assessment of disease activity essential for appropriate disease management. In particular, precise evaluation of disease activity is crucial for determining the therapeutic response to pharmacological therapy [5]. In the present cases, disease severity was classified according to the Japanese clinical severity criteria for UC [6]. Clinical assessment of UC is commonly performed using clinical activity indices such as the partial Mayo score [7], the Lichtiger index [8], and the Sutherland index [9]. In addition, leucine-rich α2-glycoprotein (LRG) is a useful biomarker for assessing disease activity [10].

Here, we report two cases in which remission was safely induced through the simultaneous initiation of CGM and systemic corticosteroids.

## Case Presentation

### Case one

A 37-year-old man visited our hospital owing to over 10 bloody bowel movements per day and lower abdominal pain for a month. He had no significant past medical, family, infectious, surgical, or psychosocial history. He smoked 10 cigarettes daily. A colonoscopy was performed, which revealed diffuse loss of vascular pattern and superficial ulcers throughout the colon (Figure *1*), and biopsies were obtained.

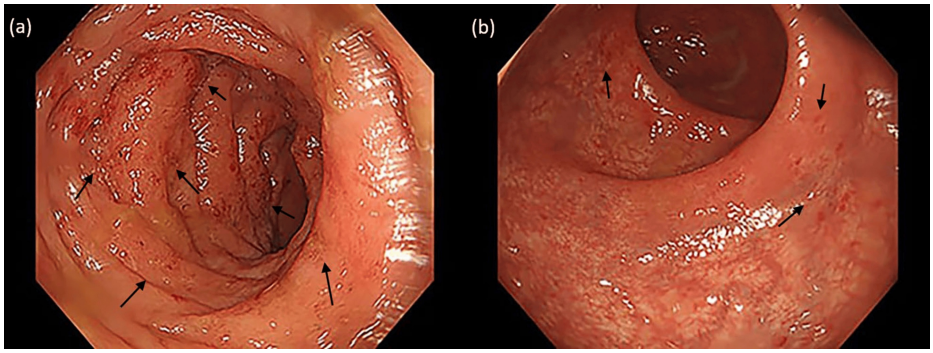



**FIGURE 1: Colonoscopy images taken at the beginning of the treatment**

The sigmoid colon (a, left panel) and rectum (b, right panel) on colonoscopy at the beginning of treatment (MES 2). Black arrows indicate inflammatory lesions. MES: Mayo endoscopic subscore.

Oral 5-aminosalicylic acid (5-ASA: 4800 mg/day) was initiated at that time. Histopathologic examination of colonic biopsies revealed chronic active inflammatory changes with lymphoid follicles. Eight days later, he was admitted with a diagnosis of UC. A colonoscopy was performed, which revealed marked erythema and an absent vascular pattern in the sigmoid colon (Mayo endoscopic subscore (MES) of two). This examination was limited to the sigmoid colon to reassess the severity of the active lesions; therefore, the extent of disease throughout the colon was not reevaluated at this examination.

On physical examination, there was no tachycardia (75 beats per minute) or fever (36.8℃). Serological examinations revealed elevated LRG (49.3 μg/mL; reference value: <16.0 μg/mL), an elevated C-reactive protein (CRP) level (3.58 mg/dL; reference range: 0.00-0.50 mg/dL), an elevated erythrocyte sedimentation rate (ESR; 30.0 mm/h), and no anemia (hemoglobin (Hb), 15.9 g/dL; reference range: 13.5-17.0 g/dL). CGM (2880 mg/day) and oral prednisolone (PSL, 30 mg/day) were started. The PSL dose was tapered off in five weeks (tapered by 10 mg/day every week up to 10 mg/day and then by half every week up to 2.5 mg), whereas oral mesalamine was continued (4800 mg once daily). Two weeks after the addition of PSL and CGM, colonoscopy showed mild erythema and a decreased vascular pattern (MES of one) (Figure *2*).

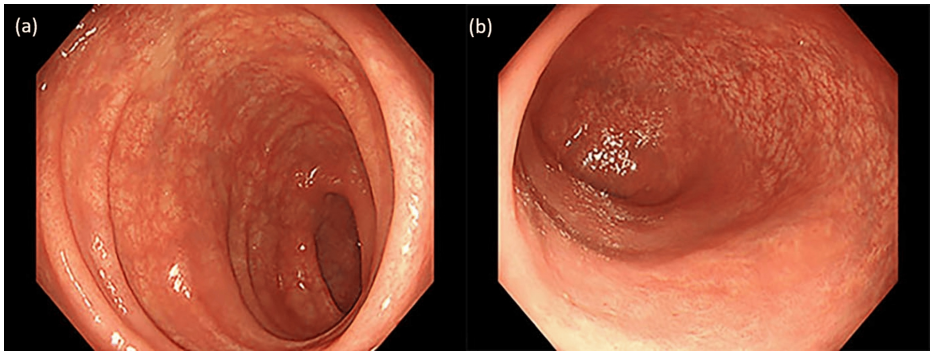



**FIGURE 2: Post-treatment colonoscony images**

The sigmoid colon (a, left panel) and rectum (b, right panel) on colonoscopy two weeks after the start of treatment (MES 1). MES: Mayo endoscopic subscore.

The patient was subsequently discharged and followed up as an outpatient. After discharge, clinical remission was maintained, with the Lichtiger index remaining at ≤one and the Sutherland index and partial Mayo score remaining at zero. Five weeks after the addition of PSL and CGM, PSL was discontinued. Thirteen weeks after the addition of PSL and CGM, colonoscopy findings showed mucosal healing, at which point CGM was discontinued. The clinical course of this case is shown in Figure *3*.

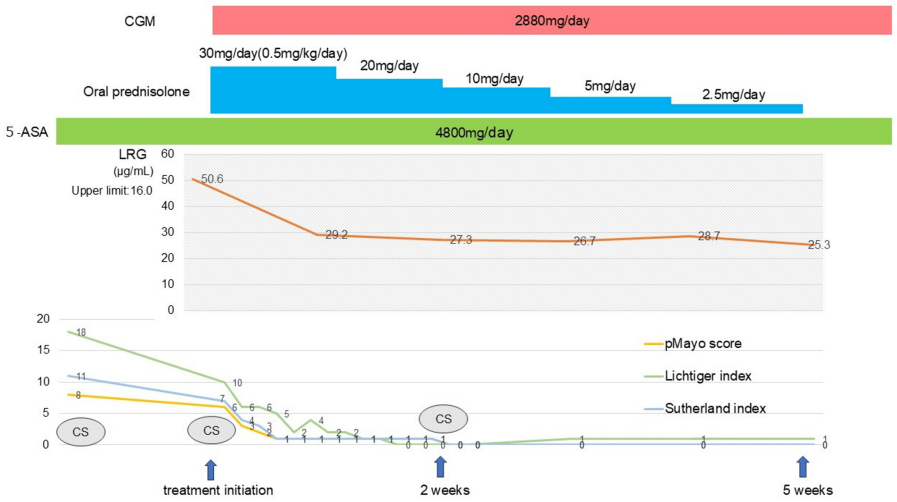



**FIGURE 3: Clinical course of case one**

CGM: carotegrast methyl; 5-ASA: 5-aminosalicylic acid; LRG: leucine-rich α2-glycoprotein; CS: colonoscopy.

## Case two

A 55-year-old man visited our hospital because of 20 bloody bowel movements per day, abdominal pain, and fever. Furthermore, he had no significant family, infectious, surgical, or psychosocial history. He smoked 15 cigarettes daily. He had visited a nearby clinic three days before presenting to our hospital. At that clinic, he was prescribed salazosulfapyridine (3000 mg/day). A colonoscopy was performed, which revealed diffuse loss of vascular pattern and superficial ulcers from the rectum to the sigmoid colon (MES of two) (Figure *4*), and biopsy samples were obtained.

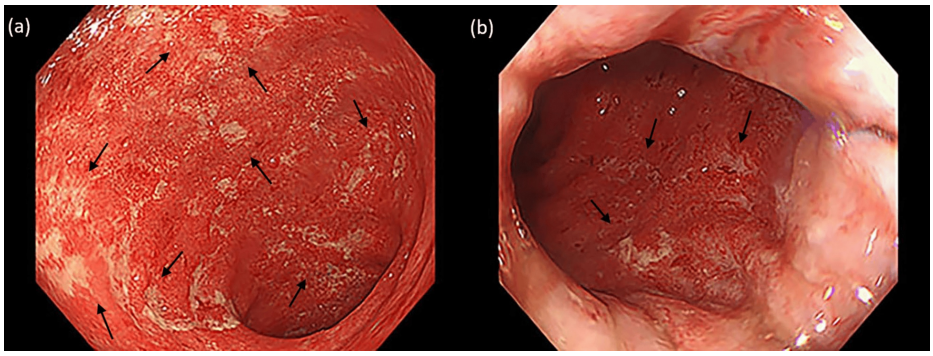



**FIGURE 4: Colonoscopy images at the beginning of the treatment**

The sigmoid colon (a, left panel) and rectum (b, right panel) on colonoscopy at the beginning of the treatment (MES 2). Black arrows indicate inflammatory lesions. MES: Mayo endoscopic subscore.

On physical examination, there was no tachycardia (86 beats per minute) or fever (36.8℃). Serological examinations revealed elevated LRG (34.0 μg/mL; reference value: <16.0 μg/mL), an elevated CRP level (3.10 mg/dL; reference range: 0.00-0.50 mg/dL), and hemoconcentration suggestive of dehydration (Hb, 18.5 g/dL; reference range: 13.5-17.0 g/dL). Histopathologic examination of the colonic biopsy samples revealed chronic active inflammatory changes, including crypt abscesses and chronic inflammatory cell infiltrates. One day later, oral 5-aminosalicylic acid (5-ASA; 4800 mg/day), CGM (2880 mg/day) and oral prednisolone (PSL, 40 mg/day) were started on admission. The PSL dose was tapered off in four weeks (tapered by 10 mg/day every five days), whereas oral 5-ASA was continued (4800 mg daily). Two weeks after the addition of PSL and CGM, colonoscopy revealed mild erythema and a decreased vascular pattern (MES of one) (Figure *5*).

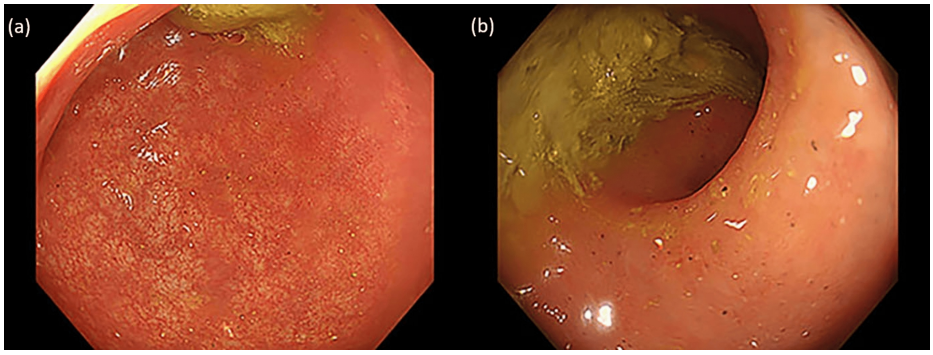



**FIGURE 5: Post-treatment colonoscopy images**

The sigmoid colon (a, left panel) and rectum (b, right panel) on colonoscopy two weeks after the start of treatment (Mayo endoscopic subscore of one).

The patient was subsequently discharged and followed up as an outpatient. Four weeks after the addition of PSL and CGM, a serological examination revealed decreased LRG levels (15.1 μg/mL). The Lichtiger index, Sutherland index, and partial Mayo score decreased after admission, and all reached zero at four weeks, at which point PSL and CGM were discontinued. The clinical course of this case is shown in Figure 6.

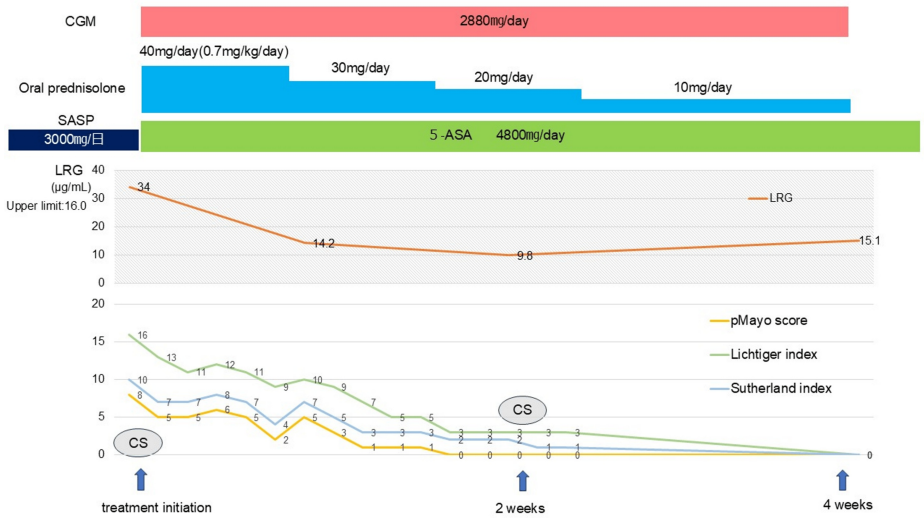



**FIGURE 6: Clinical course of case two**

CGM: carotegrast methyl; SASP: salazosulfapyridine; 5-ASA: 5-aminosalicylic acid; LRG: leucine-rich α2-glycoprotein; CS: colonoscopy.

## Discussion

This report describes two cases of successful remission induction in moderately active UC achieved through the simultaneous initiation of CGM and systemic corticosteroids. Because CGM is a relatively new therapeutic agent and the first oral agent developed in Japan [1], evidence regarding its simultaneous initiation with corticosteroids remains limited. Detailed reporting of these two cases, in which remission was safely achieved, may contribute to the accumulation of clinical experience with this novel agent. Recent real-world studies have also reported favorable clinical and endoscopic outcomes with CGM in patients with active UC, consistent with the clinical improvement observed in the present cases [4].

Corticosteroids and CGM each exert distinct pharmacological effects, acting at different stages of the inflammatory process (Figure 7).

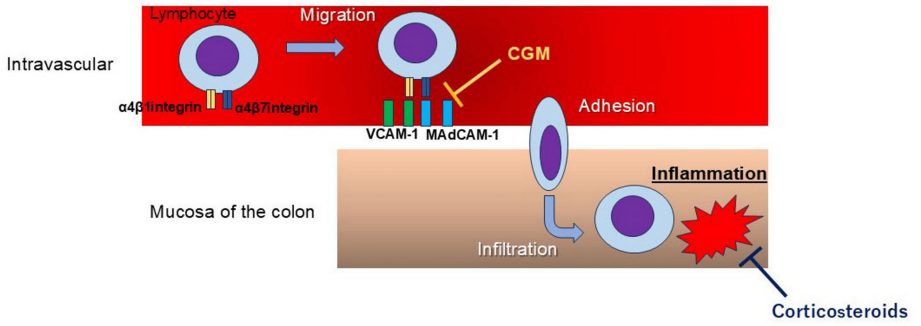



**FIGURE 7: Carotegrast methyl and corticosteroids have distinct mechanisms of action that may provide complementary therapeutic effects in ulcerative colitis**

Schematic illustration of the mechanisms of action of carotegrast methyl and corticosteroids in ulcerative colitis. The active metabolite of carotegrast selectively inhibits the binding of α4β1 integrin expressed on inflammatory cells such as lymphocytes to the adhesion molecule VCAM-1 on vascular endothelial cells, as well as the binding of α4β7 integrin to MAdCAM-1. By doing so, it suppresses the extravasation of inflammatory cells and their accumulation in intestinal tissues, thereby exerting anti-inflammatory effects. In contrast, corticosteroids primarily suppress inflammatory responses within the mucosa after immune cell infiltration has occurred.

VCAM-1: vascular cell adhesion molecule-1; MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1

Image credit: Created by the authors using Microsoft PowerPoint (Microsoft Corp., Redmond, WA, USA).

Corticosteroids primarily suppress inflammatory responses within the mucosa after immune cell infiltration has occurred; however, their long-term use is limited by adverse effects and steroid dependence [2]. In contrast, CGM inhibits lymphocyte trafficking by blocking α4β7 integrin-mediated adhesion to mucosal vascular addressin cell adhesion molecule (MAdCAM-1) on vascular endothelial cells, thereby reducing lymphocyte infiltration into the colonic mucosa [3]. The pharmacological effects of CGM, independent of corticosteroids, have the potential to yield favorable clinical results in these two cases.

One of the adverse events associated with CGM is progressive multifocal leukoencephalopathy (PML), a rare but serious opportunistic infection caused by reactivation of the John Cunningham virus [11]. In a pivotal phase three trial of CGM, concomitant use of systemic corticosteroids was permitted under predefined conditions; however, no cases of PML were reported during the study [1]. In our two cases, no adverse events, including neurological complications suggestive of PML, were observed during the combined use of CGM and systemic corticosteroids. Collectively, these findings suggest that, with careful monitoring for adverse events, further accumulation of clinical evidence is warranted to clarify the potential risk of infection and the long-term safety of concomitant CGM and corticosteroid therapy.

There are limitations to these case reports. First, as this report includes only two patients, the efficacy of simultaneous initiation of CGM and corticosteroids cannot be established, and a causal relationship between this treatment strategy and the observed clinical improvement cannot be determined. In addition, the rapid improvement observed in these cases may have been largely attributable to corticosteroids, and the relative contribution of CGM cannot be clearly distinguished. Second, there was no predefined uniform criterion for discontinuing CGM, and the timing of discontinuation was determined individually based on the overall clinical course in each case. Third, concomitant 5-ASA and/or sulfasalazine may have contributed to the observed improvement; therefore, the effects cannot be attributed solely to CGM and corticosteroids.

## Conclusions

We report two cases of moderately active UC in which remission was successfully achieved through the simultaneous initiation of CGM and systemic corticosteroids. Both patients showed rapid clinical and endoscopic improvement, allowing for early steroid tapering and discontinuation without relapse or serious adverse events. Given the distinct and potentially complementary mechanisms of action of corticosteroids and CGM, their simultaneous initiation may represent a promising induction strategy in selected patients. Larger prospective studies are needed to establish the efficacy, safety, and optimal positioning of this therapeutic approach in the treatment algorithm for UC.

## Additional Information

## Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Tsuyoshi Suda, Kiichiro Kaji, Kuniaki Arai, Shuichi Terasaki

**Acquisition, analysis, or interpretation of data:** Tsuyoshi Suda, Haruo Oka, Miyabi Miura

**Critical review of the manuscript for important intellectual content:** Tsuyoshi Suda, Miyabi Miura, Kiichiro Kaji, Kuniaki Arai, Shuichi Terasaki

**Drafting of the manuscript:** Haruo Oka

## Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** Tsuyoshi Suda has received lecture honoraria from Kissei Pharmaceutical Co., Ltd. and Zeria Pharmaceutical Co., Ltd. All other authors have no conflicts of interest to declare. **Financial relationships:** Tsuyoshi Suda declare(s) personal fees from Kissei Pharmaceutical Co., Ltd. Tsuyoshi Suda has received lecture honoraria from Kissei Pharmaceutical Co., Ltd. Tsuyoshi Suda declare(s) personal fees from Zeria Pharmaceutical Co., Ltd. . Tsuyoshi Suda has received lecture honoraria from Zeria Pharmaceutical Co., Ltd. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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