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Induction of Remission and Maintenance Therapy with Tacrolimus in Refractory Ulcerative Colitis with Adverse Events from 5-ASA and Thiopurine

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Abstract

A 58-year-old Japanese woman was admitted to the hospital with fever, diarrhea, melena and lower abdominal pain. Colonoscopy showed moderate left-sided Ulcerative Colitis (UC). Administration of 5-aminosalicylic acid (5-ASA) (3600 mg) was started, but skin eruptions and hepatic dysfunction occurred. The drug lymphocyte stimulation test (DLST) was positive for 5-ASA, so this medication was discontinued. Prednisolone (PSL, initially 10 mg/day) was started, and remission was achieved. However, relapse occurred 5 months later after the discontinuation of PSL, and hospitalization was required again. Remission was achieved again by PSL, and azathioprine (AZA) (initially 25 mg/day) was started as maintenance therapy. Hepatic dysfunction was detected at 1 month after starting AZA and was judged to represent drug-induced hepatitis. Following the discontinuation of AZA, PSL (2 mg/day) monotherapy was continued. At 11 months after discharge from hospital, the patient developed diarrhea, melena, and abdominal pain, requiring hospitalization for the third time. Colonoscopy showed extensive ulceration and spontaneous bleeding, indicating a relapse of severe UC. Administration of tacrolimus (TAC) led to remission and the patient was discharged from hospital. Because she experienced adverse effects with 5-ASA and AZA, TAC alone was continued as maintenance therapy for ≥ 2 years after the discontinuation of PSL. Relapse did not occur during this period and repeat colonoscopy showed mucosal healing. During the TAC maintenance therapy, slight deterioration of renal function was observed, but there were no other adverse events. In conclusion, we experienced a rare patient who responded to TAC maintenance monotherapy for severe UC.

Keywords: Ulcerative colitis; Tacrolimus; Remission; Tacrolimus maintenance therapy

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with remissions and relapses. Tacrolimus (TAC) and biological agents for refractory UC have recently broadened the options for remission induction therapy. TAC in particular has been reported to achieve a high remission rate in patients with refractory UC (1). However, it is unclear whether TAC is effective as maintenance therapy.

We treated a patient with UC for whom the maintenance of remission was difficult to achieve, due to her associated adverse reaction to common medications used for maintenance therapy. The patient has maintained long-term remission on TAC monotherapy as of the time of this writing, 3 years after the initiation of the TAC monotherapy. We report this case and provide a brief literature review.

Case Report

The patient was a 58-year-old Japanese woman whose extensive UC had been diagnosed 1 year prior to her first visit to our hospital with fever (temperature>38°C), diarrhea (6–7 times/day), melena (3–4 times/day), and lower abdominal pain. She was diagnosed with moderate left-sided UC by colonoscopy/histopathology and was admitted to the hospital due to persistent fever (>38°C). After admission, 5-ASA (3600 mg/day) was started, but a few days later eruptions appeared on her neck, and liver function tests showed elevated values. A Drug Lymphocyte Stimulation Test (*DLST*) was positive for 5-ASA, and we therefore discontinued this drug. Administration of prednisolone (PSL, 10 mg/day) was started, but it did not improve the diarrhea, melena and abdominal pain. In addition, bilateral knee pain and coin-shaped erythema nodosum on both lower extremities were noted at 10 days after admission. These symptoms were considered extra intestinal complications of UC, so PSL was increased to 40 mg/day. After this dosage increase, the diarrhea, melena, abdominal pain, fever, and joint pain improved rapidly. PSL was gradually tapered to 20 mg/day, and the patient was discharged from hospital. Three months later, the administration of PSL was discontinued and the patient received no other therapy. Two months after the discontinuation of PSL, diarrhea (8–9 times/day), melena (5–6 times/day), and lower abdominal pain appeared again.

She was admitted to our hospital a second time with a relapse of UC. Colonoscopy showed moderate UC (Figure 1), and thus she was treated with 30 mg/day PSL. This resulted in an immediate improvement of clinical signs and symptoms, and the administration of azathioprine (AZA, 25 mg/day) was started as maintenance therapy 2 weeks later. Since no adverse effects were observed, the dosage of AZA was increased to 50 mg/day and the patient was discharged from the hospital. At 1 month after the start of AZA therapy, liver dysfunction was detected (T-bil, 0.8 mg/dL; D-bil, 0.1 mg/dL; AST, 117 U/l; ALT, 165 U/l; ALP, 2381 U/l; γ-GTP, 2420 U/L; and PT>100%). Tests for autoantibodies and markers of hepatitis virus B and C were negative. The latter changes were considered to be due to drug-induced hepatitis, and the AZA was therefore discontinued. The liver function improved after the discontinuation of AZA. PSL was gradually tapered to 2 mg/day by 8 months after the start of its administration. Although we recommended treatment with a biological agent during the gradual tapering of PSL, the patient refused such therapy. Therefore, the administration of PSL (2 mg/day) was continued.

At 11 months after the second discharge, the patient's UC relapsed with abdominal pain, diarrhea, and melena. She was admitted to our hospital for a third hospitalization. The findings included height of 158

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Laboratory findings	Values	Units
WBC count	9.18×10^3	μL
Neutrophils, %	77.2	%
Lymphocytes, %	16.8	%
Hemoglobin	11.3	g/dL
Platelet count	52.9×10^4	μL
Coagulation factors		
Prothrombin time %	100	%
D-dimer	1.4	μg/ml
Biochemical tests		
TP	6.5	g/dl
ALB	2.8	g/dl
T-Bil	0.3	mg/dl
AST	17	IU/l
ALT	11	IU/l
ALP	206	IU/l
γGTP	37	IU/l
LD	168	IU/l
BUN	9.1	mg/dl
Cre	0.65	mg/dl
eGFR	71.6	ml/min
Na	142	mEq/l
K	4.1	mEq/l
CL	102	U/l
TG	141	mg/dl
HDL	44	mg/dl
CRP	1.07	mg/dl
Infection		
CMVAgC7-HRP	(−)	--
T-SPOT.Tb	(−)	--
Stool culture	(−)	--

Table 1. Laboratory findings on admission.

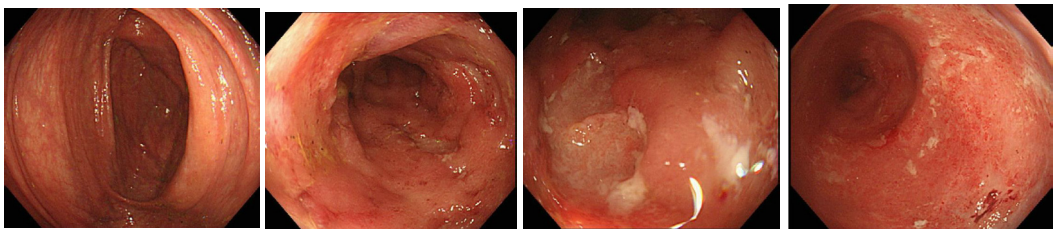
cm, weight 46 kg, blood pressure 122/72 mmHg, and pulse rate 70/min. The body temperature was 36.8°C. The stool frequency was 8–10 times/day and the frequency of melena was 4–5 times/day, with no defecation at night.

The physical examination showed redness of the skin with no swelling. The abdomen was flat and soft, with moderate tenderness in the sub-umbilical region. Laboratory tests showed Hb of 11.3 g/dL (anemia), and the white blood cell count was increased to 9180/μl, though the platelet count was increased to 529,000/μl. Biochemical tests showed a decrease in serum albumin to 2.8 mg/dL, with the CRP of 1.07 mg/dL, and high levels of certain inflammatory parameters. Coagulation tests showed an increase in D-dimer (up to 1.4 μg/mL). A stool culture showed normal bacterial flora only (Table 1).

Colonoscopy findings: A colonoscope was inserted to the cecum. Deep ulceration, severe mucosal edema, and easy bleeding on contact with the scope were observed from the transverse colon (a) to the sigmoid colon. Mucosal edema, small ulcers, and adhesions of mucosa were observed in the rectum (Figure 1).

After the third admission: Based on the colonoscopy findings of severe mucosal edema, deep ulceration, and easy bleeding in the left colon, we diagnosed a relapse of severe UC. A central venous catheter was inserted, and we initiated a nil oral regimen. Treatment with PSL (30 mg/day) and TAC blood trough (10-15 ng/mL) was started. The TAC trough level was high at 2 days after the start of the administration, and the Lichtiger score (for the clinical evaluation of the severity of UC) was 4 at 7 days after the start of TAC therapy, indicating that remission was achieved [1,2].

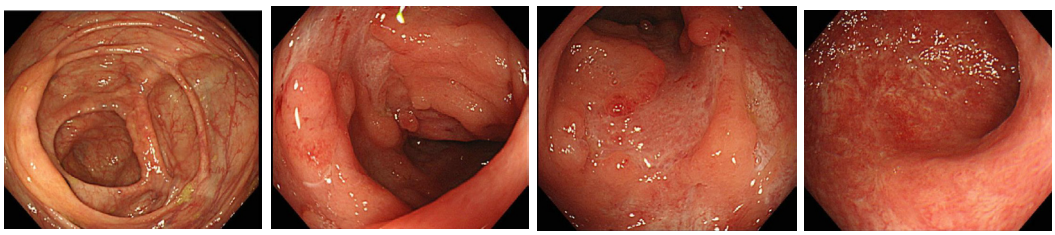
Colonoscopy was repeated 15 days after the start of TAC administration. The mucosal edema and easy bleeding had improved, and a regression of ulceration and mucosal healing in the ulcer bases was observed (Figure 2). These findings suggested a complete response to the TAC. Accordingly, oral intake of food was started and the PSL



Ascending colon Transverse Colon Sigmoid colon Rectum

Note: Observation up to the ascending colon. Extensive undermining ulcers, severe mucosal edema, and scope contact-induced hemorrhage were observed in the transverse colon over the sigmoid colon. Although mucosal edema was present in the rectum, only partial visible vascular patterns and erosion were observed.

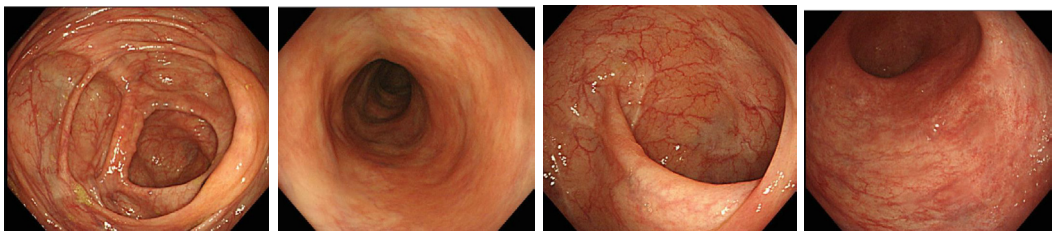
Figure 1: Pre-treatment colonoscopic findings as far as the transverse colon.



Ascending colon Transverse Colon Sigmoid colon Rectum

Note: Observation up to the ascending colon. In the transverse~sigmoid colon edema was moderate and extensive ulcers were observed. However, the mucosa of the ulcer floor was regenerated. In rectum, only partial reddening was noted.

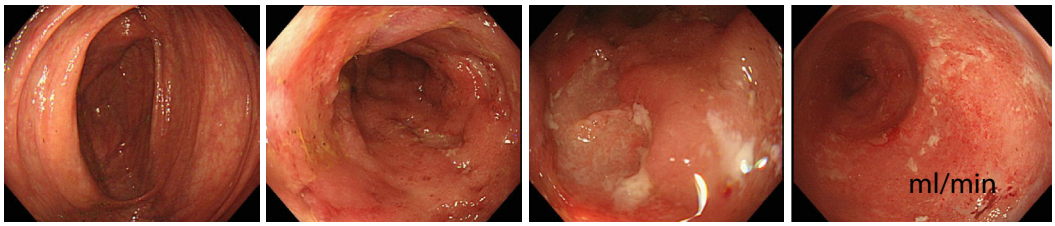
Figure 2: Colonoscopic findings at 2 weeks after the start of TAC treatment.



Ascending colon Transverse colon Sigmoid colon Rectum

Note: Observation up to the ascending colon. In the transverse~sigmoid colon, ulcer scars were noted. Visible vascular patterns were partially improved. Rectal erosion had resolved as compared with findings of previous as colonoscopy.

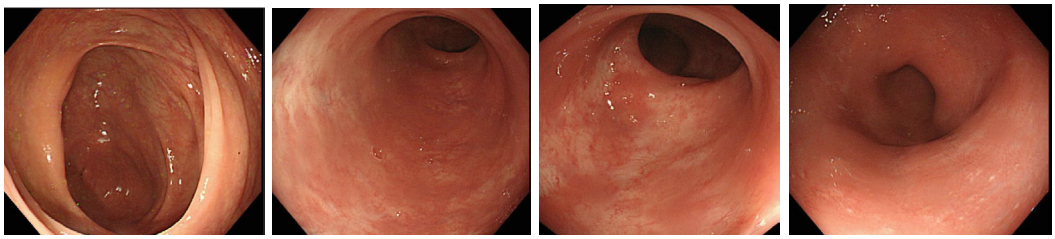
Figure 3: Colonoscopic findings at 12 weeks after the start of TAC treatment.



Ascending colon Transverse colon Sigmoid colon Rectum

Note: Observation up to the ascending colon. In the transverse~sigmoid colon reddening was partially noted, however visible vascular patterns were improved. Healed mucosa was noted in the rectum.

Figure 4: Colonoscopic findings at 24 weeks after the start of the treatment.



Ascending colon Transverse colon Sigmoid colon Rectum

Note: Observation up to the ascending colon. Healed mucosa was noted in the total colon.

Figure 5: Colonoscopic findings at 96 weeks after the start of the TAC treatment.

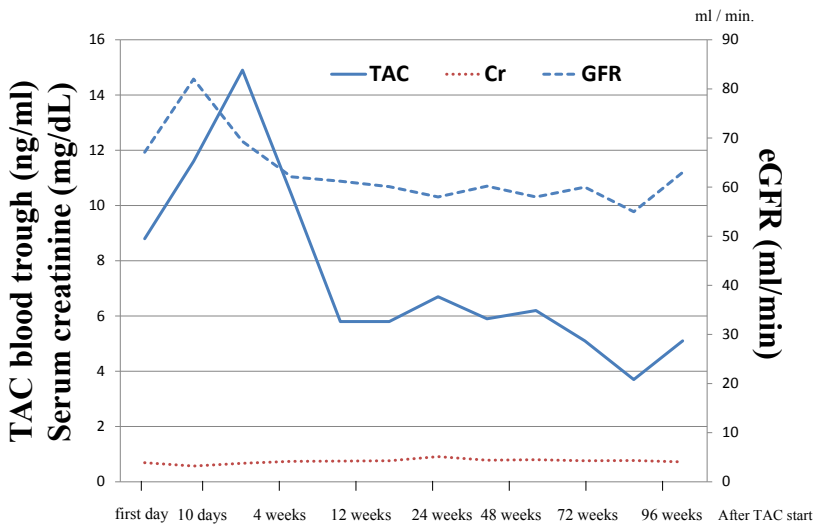


Figure 6: Serial changes in the TAC blood trough, serum creatinine, and eGFR.

was decreased by 10 mg every week. The patient was discharged from the hospital at 30 days after starting TAC, by which time the PSL dose had been decreased to 10 mg/day. Colonoscopy was performed again 3 months after the start of TAC therapy and showed mucosal healing (Figure 3), confirming the induction of remission by the TAC. The administration of TAC was continued, and the PSL was gradually tapered and discontinued. Maintenance therapy with TAC alone was continued for 3 years. During this period, relapse did not occur and colonoscopy continued to show mucosal healing (Figures 4 and 5). During maintenance therapy with TAC blood trough (5-10 ng/mL) alone, mild renal dysfunction was observed, but there were no other adverse effects (Figure 6).

Discussion

The treatment of UC is selected based on its clinical and endoscopic severity, as well as the therapeutic response to PSL (3). In our patient, 5-ASA was used during the initial treatment, but allergy and hepatic dysfunction occurred. Subsequently, remission was achieved with PSL alone, but relapse occurred after the discontinuation or decrease of PSL. Remission was achieved again after resuming treatment with PSL, and thus an administration of AZA was started as maintenance therapy [3,4]. However, hepatic dysfunction occurred after the AZA was started, and thus we discontinued it and the patient's liver dysfunction resolved spontaneously. PSL monotherapy was started subsequently but relapse occurred. The second relapse was severe both clinically and endoscopically. Therefore, TAC add-on therapy was used for the steroid-dependent refractory UC [4,5].

AZA could not be used because the patient showed signs of allergic reactions. Therefore, after the induction of remission with TAC, we considered maintenance therapy with a biological agent [6]. However, the patient had several drug allergies and she was anxious about using a new medication, which made it difficult to start the use of a biological drug. In addition, she had no allergic reaction to TAC and no adverse events were observed. Accordingly, we used TAC as the maintenance therapy. During the maintenance therapy with TAC, only minor renal dysfunction was observed. The trough levels of TAC and the changes of renal function are shown in (Figure 6).

In this patient, no adverse effects apart from minor renal dysfunction were observed during the long-term administration of TAC. This suggested the possible safety of the long-term use of this drug [7].

Several studies have reported that TAC achieves a high remission rate when used for remission induction therapy in patients with severe refractory UC. Generally, AZA is used to maintain the remission of UC after remission induction by TAC [3,4,8]. However, it has been reported that in patients with adverse effects due to AZA, TAC alone was used as maintenance therapy or long-term TAC was used concomitantly with AZA to maintain remission [9]. In our patient, remission was maintained by a long-term administration of TAC alone, which is a rare. Because our patient had an allergic reaction to 5-ASA, it was difficult to use it concomitantly with TAC.

In the treatment of UC, 5-ASA derivatives are usually used for both remission induction and maintenance therapy as first-line drugs and are used concomitantly with a variety of other agents [10]. Consequently, using TAC alone without a 5-ASA derivative is rare. The present case suggests that TAC alone can be used as maintenance therapy. In patients who do not tolerate AZA, TAC can be used for both the induction of remission and maintenance therapy.

A long-term administration of TAC may cause renal damage [11], and thus a careful monitoring of renal function is necessary under such treatment. The development of renal dysfunction requires the discontinuation of TAC and a switch to a biological agent for maintenance therapy.

Conclusion

We treated a rare patient with severe UC in whom remission was induced by TAC and subsequent maintenance therapy was achieved under the control of TAC alone.

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