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【 CASE REPORT 】

Refractory Ulcerative Colitis Improved by Scheduled Combination Therapy of Vedolizumab and Granulocyte and Monocyte Adsorptive Apheresis

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Abstract:

Granulocyte and monocyte adsorptive apheresis (GMA) is occasionally introduced as an alternative combination therapy after loss of response to biologics in ulcerative colitis (UC) patients. However, there have been no reports of the concomitant use of vedolizumab (VDZ) and GMA for the initial induction of UC. A 20-year-old man with refractory UC was admitted for recrudescence. VDZ monotherapy had previously been introduced but was ineffective. Therefore, he received scheduled combination of VDZ and GMA and achieved clinical remission. The combination of two different approaches to inhibit the migration of leukocytes into the inflamed tissue led to satisfactory clinical outcomes.

Key words: apheresis, clinical remission, ulcerative colitis, vedolizumab

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Introduction

Vedolizumab (VDZ), a gut-selective blocker of lymphocyte trafficking, was administered to patients with ulcerative colitis (UC) in the active phase in an international randomized, double-blind, placebo-controlled trial (RCT), and the response rates of induction therapy at week 6 were 47.1% and 25.5% in the VDZ group and placebo group, respectively (1). Another RCT was conducted for Japanese UC patients that also showed a non-significantly greater efficacy than placebo as induction therapy (39.6% vs. 32.9% at week 10; p = 0.2722) (2). Therefore, the clinical efficacy of VDZ as induction therapy has not been fully clarified for Japanese patients, especially for those who need hospitalization.

The combination of granulocyte and monocyte adsorptive apheresis (GMA) with anti-tumor necrosis factor (TNF) agents is considered to be effective after loss of response to anti-TNF agents in UC. Rodríguez-Lago et al. reported that 32% of patients responded to combination therapy, showing a dramatic reduction in the median fecal calprotectin level in one month without intensification, switch, or swap of anti-TNF agent or colectomy (3). They also reported that GMA was started after a loss of response to VDZ in 8 patients, and 3 (38%) achieved steroid-free clinical remission, while 5 (63%) withdrew from VDZ (4). Sáez-Gonzáleza et al. reported that a patient maintained clinical and biological activity despite having started VDZ in combination with azathioprine for six months following steroid therapy and achieved clinical remission after combining GMA with VDZ (5).

These findings suggest that refractory UC may be able to be improved by simultaneous GMA with an initial biologic induction therapy. We herein report a long-standing active UC patient whose disease activity and endoscopic findings improved by scheduled combination of VDZ and GMA.

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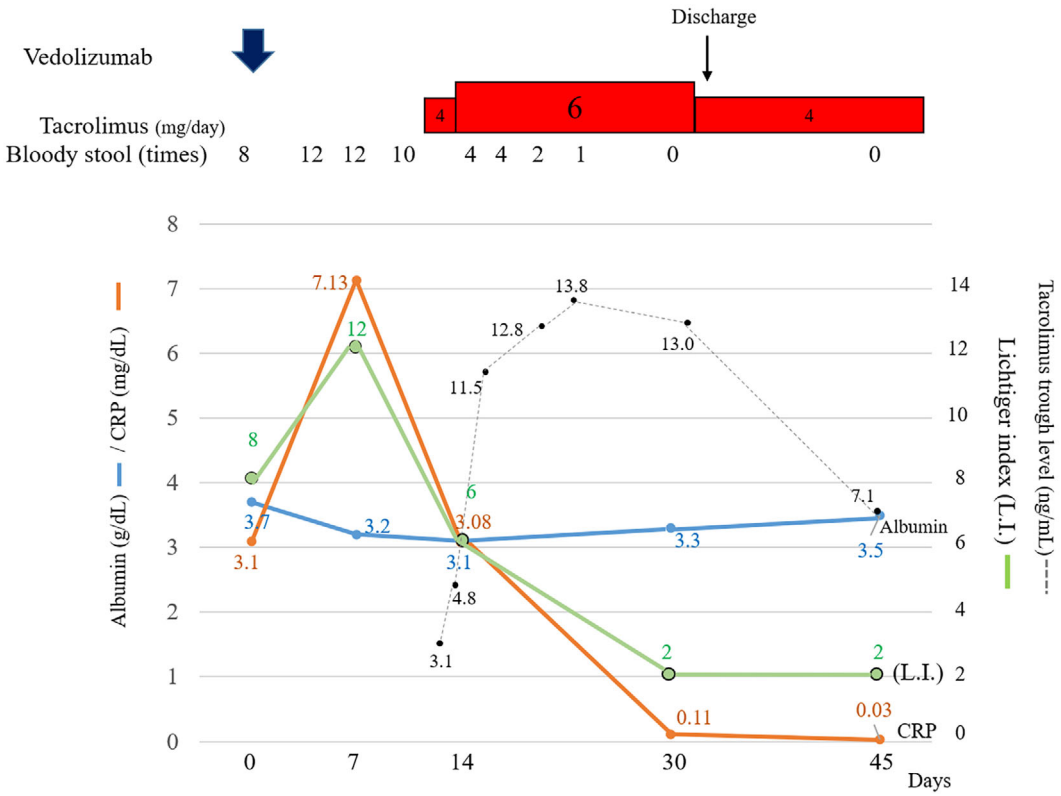

Figure 1. **Clinical course the previous time.**

Case Report

A 20-year-old man developed UC at 15 years of age and had a history of emergency hospitalization (3 times). His UC was the relapse-remitting total colitis type with moderate disease activity. He had serious allergic reactions to mesalazine and infliximab. He had also developed pericarditis by the administration of mesalazine.

At his second admission, he was started on an immunomodulator with steroid therapy. He subsequently achieved steroid-free remission for one year. However, he relapsed with a Lichtiger index score of 8 points and serum C-reactive protein level of 3.1 mg/dL at the third admission (Fig. 1). He received VDZ as an induction therapy this time because of his allergies to infliximab but showed little response. Subsequent administration of tacrolimus with a high trough level was effective, and he was discharged two weeks after the induction. During 3 months of the tacrolimus administration with clinical and endoscopic remission, he was administered 75 mg of azathioprine every day for 1 year.

However, he was admitted again 269 days after the discontinuation of tacrolimus due to increasing UC activity, with a Lichtiger index score of 10 points (Fig. 2). Sigmoidoscopy showed an Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score of 4 points (vascularity 2, bleeding 1, erosion and ulceration 1) with several small ulcerations (Fig. 3). The patient characteristics are shown in Table 1, and the laboratory data are shown in Table 2. Because the previous administration of VDZ had caused no adverse events and there was evidence for the usefulness of GMA with an anti-TNF agent (a kind of biologic), we prescribed scheduled combination therapy of VDZ and GMA after obtaining his informed consent.

He received semiweekly sessions via peripheral venous access using a GMA device (Adacolumn®; JIMRO, Takasaki, Japan) starting the day after the first VDZ administration. His watery stool decreased gradually within one week. On days 10 and 20, his UCEIS scores became 1 point (1, 0, 0) (Fig. 4) and 0 points (Fig. 5), respectively, which was defined as mucosal healing. He was discharged on day 22 and was able to maintain clinical remission by VDZ monotherapy for six months.

Discussion

VDZ inhibits the interaction between a4b7 integrin and mucosal addressing cell adhesion molecule-1, which is selectively expressed by the vascular endothelium in the gastrointestinal tract. No significant differences were reported in the clinical results between infliximab and VDZ for inducing remission (6). Given the efficacy and safety of VDZ, this agent seems to be a favorable therapeutic option in patients with UC who have shown a lack of response to glucocorticoids, immunomodulators, and anti-TNF agents.

Real-world experience studies for VDZ have shown that a clinical response and remission were achieved in 43% [95% confidence interval (CI) 0.37-0.49] and 25% (95% CI 0.12-0.45) by Week 6, respectively, and in 51% (95% CI 0.43-0.61) and 30% (95% CI 0.24-0.36) by Week 14, respec-

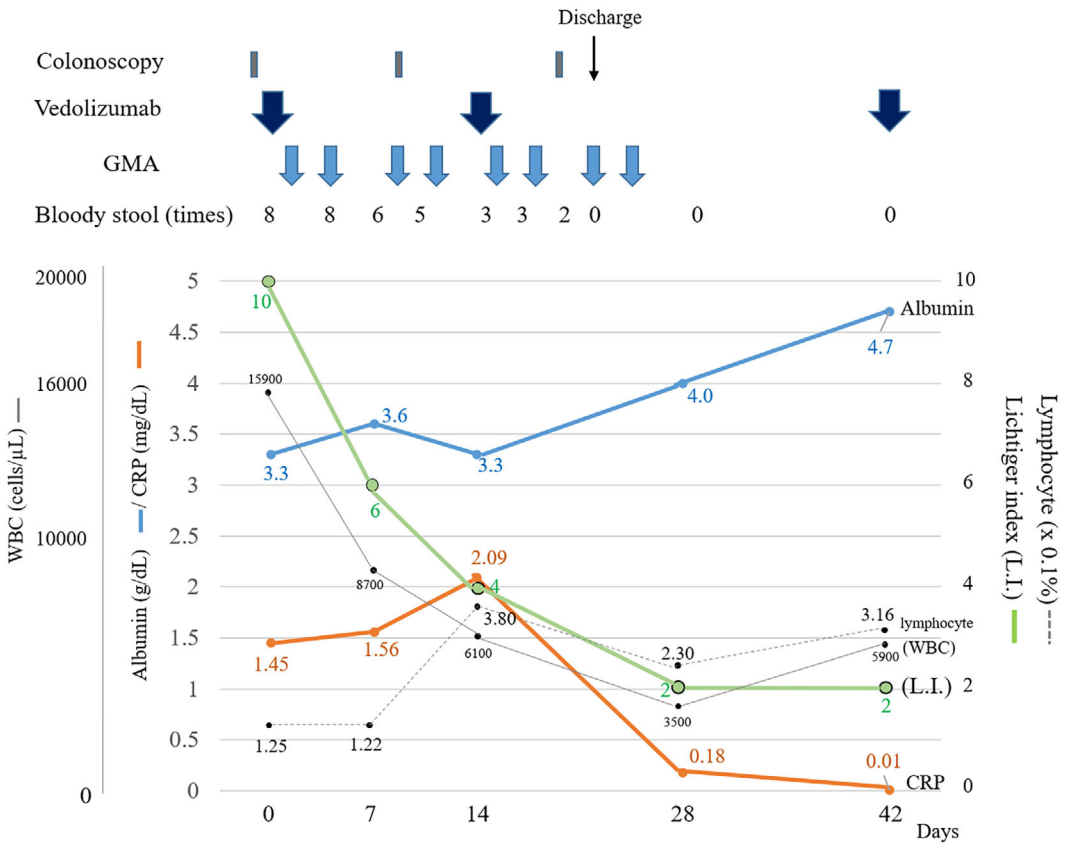

Figure 2. **Clinical course the present time. GMA: granulocyte and monocyte adsorptive apheresis**

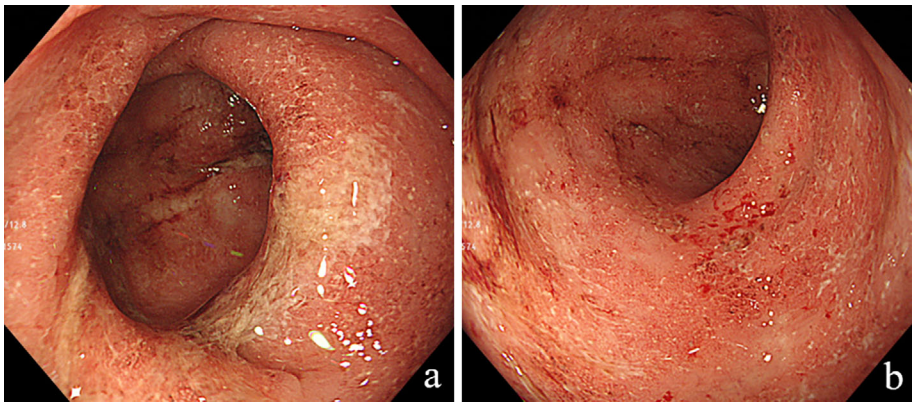

Figure 3. **a: Day 0, Sigmoid colon/edematous, complete loss of vascular pattern, coagulated blood, and tiny defects in the mucosa. UCEIS 4 (2,1,1). b: Day 0, Rectum/edematous, complete loss of vascular pattern, some bleeding spots and tiny defects in the mucosa. UCEIS 4 (2,1,1).**

tively (7). Regarding predictors of the clinical response to VDZ, Amiot et al. reported that the clinical response at week 6, baseline C-reactive protein (CRP) >20 mg/L, and a high baseline disease activity were predictive of steroid-free remission at week 14 (8). Another multi-variable analyses showed that prior exposure to an anti-TNF agent was associated with a reduced probability of achieving clinical remission [hazard ratio (HR) 0.53, 95% CI 0.38-0.75] and endoscopic remission (HR 0.51, 95% CI 0.29-0.88) by VDZ induction (9). The moderate-to-high disease activity and exposure to infliximab (although allergic reaction occurred) in this patient may be consistent with the risk factors known to be associated with a poor response to VDZ.

This patient received scheduled combination therapy with VDZ and GMA, which can lead to clinical remission. Our search of the literature revealed no report on the use of this combination therapy for initial induction and achievement of clinical remission, although several studies described the effectiveness of optional GMA after loss of response to biologics (3-5). The beneficial effects of this combination therapy may involve multiple mechanisms of action. One hypothesized mechanism was based on the improvement in

Table 1. The Patient Characteristics.

Items	Data
Nationality	Japanese
Age	20 years old
Gender	Male
Type	total colitis, relapse-remitting
Duration	5 years
Family history	none
Personal history	pericarditis
Smoking	never
Drinking	rarely
Job	unemployed
Previous admission	3 times
Lichtiger index	10
UCEIS	4

UCEIS: Ulcerative Colitis Endoscopic Index of Severity

Table 2. Laboratory Data on Admission.

Parameter	Data	Normal range
WBC (cells/μL)	15,900a	3,300–8,600
Neut (%)	64.5	38–74
Lym (%)	12.5b	16.5–49.0
RBC ($\times 10^6$/μL)	4.57	4.35–5.55
Hb (g/dL)	12.2b	13.7–16.8
Ht (%)	37.0b	40.7–50.1
Plt ($\times 10^3$/μL)	460a	158–348
TP (g/dL)	6.4b	6.6–8.1
Alb (g/dL)	3.3b	4.1–5.1
AST (U/L)	8b	13–30
ALT (U/L)	3b	10–42
LD (U/L)	132	124–222
ALP (U/L)	145	106–322
γ-GTP(U/L)	12b	13-64
T.Bil (mg/dL)	0.4	0.4–1.5
CK (U/L)	40b	59–248
Amy (U/L)	56	44–132
UN (mg/dL)	2.9b	8.0–20.0
Cr (mg/dL)	0.75	0.65–1.07
Na (mmol/L)	139	138–145
K (mmol/L)	3.7	3.6–4.8
Cl (mmol/L)	102	101–108
FBS (mg/dL)	95	73–109
CRP (mg/dL)	1.45a	<0.14
ESR, 60 min (mm)	23a	3–15
HBs-Ag	(−)	(−)
HCV Ab	(−)	(−)
HIV-1/2 Ab	(−)	(−)
CMV-Ag	(−)	(−)
T-SPOT.TB	(−)	(−)

[a]Increased compared with the normal range.
[b]Decreased compared with the normal range.
Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, Amy: amylase, AST: aspartate aminotransferase, Cl: chloride, CK: creatine kinase, CMV: cytomegalovirus, Cr: creatinine, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, FBS: fasting blood glucose, γ-GTP: gamma-glutamyl transpeptidase, Hb: hemoglobin, HBs-Ag: hepatitis virus B surface antigen, HCV: hepatitis C virus, HIV: human immunodeficiency virus, Ht: hematocrit, K: potassium, LD: lactate dehydrogenase, Lym: lymphocyte, Na: sodium, Neut: neutrophil, Plt: platelet, RBC: red blood cell, T.Bil: total bilirubin, T-SPOT.TB: tuberculosis specific interferon-γ releasing assay, TP: total protein, UN: urea nitrogen, WBC: white blood cell

the blood trough levels of the drugs, reduction in anti-drug antibodies, or both, in response to the induction of GMA (3). Notably, GMA after loss of response to infliximab did induce in an increase in the blood trough levels of infliximab (10). Shimoyama et al. further showed that GMA induced the suppression of cytokine production by investigating the blood concentration of inflammatory cytokines at pre- and post-GMA (11). Tanida et al. reported on scheduled combination therapy with tofacitinib, a small-molecule inhibitor of Janus kinases, plus intensive GMA for induction, and the rate of clinical remission at 10 weeks was 71.4% in 7 patients (12). They suggested that the combination therapy worked by drastically downregulating the circulating inflammatory cytokines and the expression of adhesive molecules on activated granulocytes (an effect of GMA) and by downregulating the local inflammatory cytokines at the microenvironmental sites in the gut mucosa (an effect of tofacitinib), thereby inducing rapid and good clinical remission.

In contrast to these previously reported combinations, VDZ and GMA were able to strengthen the suppression of the migration of leukocytes into the inflamed tissue by combining their mechanisms of action, as the migration of peripheral inflammatory cells from the blood vessels is blocked by VDZ, and multiple immune cells-including the congested ones in the peripheral blood-can be removed by GMA. Saniabadi et al. reported that GMA was able to deplete activated myeloid lineage leucocytes, the sources of pro-inflammatory cytokines, which damaged intestinal mucosa indirectly (13). Therefore, introduction of GMA has the potential to exert additional effects as induction therapy with biologics.

Regarding the clinical course, we examined whether or not combination therapy rapidly worked for this patient. In Fig. 2, the Lichtiger index score and his bloody stool improved in the initial two weeks, while the serum CRP and albumin levels improved after the second round of VDZ administration. This treatment course was considered to be due to the effect of VDZ itself as well as combination therapy. Liefferinckx et al. reported the impact of VDZ trough levels during induction therapy period for the clinical course of UC (14). In the present case, the biomarkers were considered to have improved with the increase in the trough level of VDZ by the second administration.

The present patient had previously failed maintenance therapy with an immunomodulator. In a large, real-world cohort of VDZ therapy, the relationship between successful maintenance therapy and deep remission according to CRP

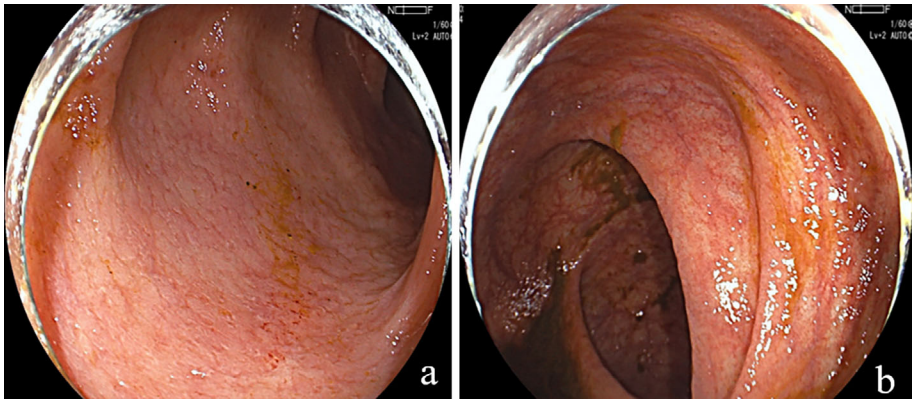

Figure 4. **a: Day 10, Sigmoid colon less edematous, but the surface remained rough. Blurring of vascular pattern. UCEIS 1 (1, 0, 0). b: Day 10, Rectum/nearly achieving mucosal healing. Blurring of vascular pattern. UCEIS 1 (1, 0, 0).**

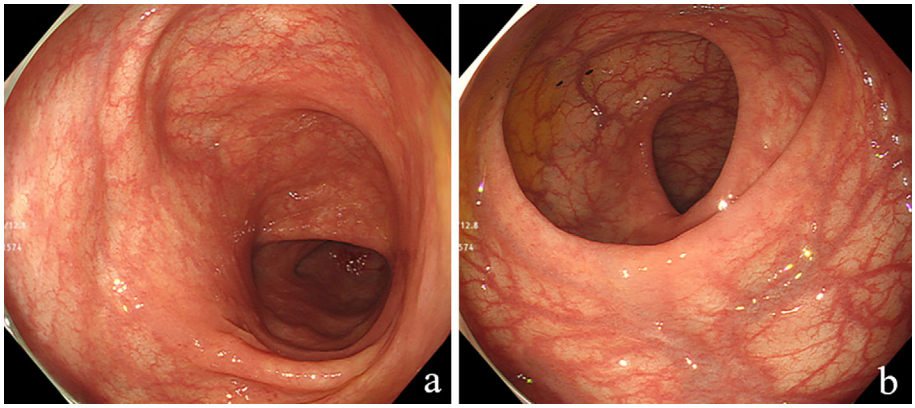

Figure 5. **a: Day 20, Sigmoid colon achieved mucosal healing. UCEIS 0. b: Day 20, Rectum/achieved mucosal healing. UCEIS 0.**

levels and endoscopy findings in UC was revealed (15). VDZ may be useful for maintenance therapy of UC in the long term (2). This patient is expected to maintain clinical remission, since he achieved mucosal healing and a normal range of CRP levels.

In conclusion, scheduled combination therapy of VDZ and GMA may be a viable alternative strategy for patients with a high potential risk of initial failure of biologics.

The authors state that they have no Conflict of Interest (COI).

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