ORIGINAL PAPER

Nagoya J. Med. Sci. **86**. 407–421, 2024
doi:10.18999/nagjms.86.3.407

# Predictors of the efficacy of vedolizumab in patients with ulcerative colitis

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## ABSTRACT

Vedolizumab is a treatment option for ulcerative colitis but data on predictors of treatment response remain insufficient to establish personalized treatment strategies. We aimed to investigate the real-world effectiveness of vedolizumab in adult patients with ulcerative colitis and explore factors involved in predicting treatment response. This single-center, single-arm, prospective observational study included 26 patients with clinically active ulcerative colitis patients' characteristics at baseline, epidemiological information, existing treatment, clinical activity index score, endoscopic score, and blood test data were collected. Serum levels of tumor necrosis factors alpha, interferon gamma, interleukin-4, interleukin-6, interleukin-10, interleukin-17, soluble mucosal addressin cell adhesion molecule 1, and soluble vascular cell adhesion molecule 1 were measured. Patient characteristics in the remission and non-remission groups were compared based on these parameters. Clinical remission at 6 weeks of treatment occurred in 9 (35%) of the 26 patients. At 14 weeks, clinical remission was observed in 11 patients (42%). There were no significant differences pertaining to age, sex, duration of disease, extent of disease, steroid resistance, or prior treatment with biological agents among the two groups after 14 weeks of treatment. Hemoglobin ≥ 11.5 g/dL (odds ratio, 15.0; 95% confidence interval, 1.50–149; P=0.014) and soluble mucosal addressin cell adhesion molecule 1 ≥ 765 pg/mL (odds ratio, 17.3; 95% confidence interval, 2.36–127; P=0.004) were significant factors. In conclusion, hemoglobin and serum soluble mucosal addressin cell adhesion molecule 1 levels are factors correlated with the therapeutic efficacy of vedolizumab.

Keywords: ulcerative colitis, vedolizumab, predictive factor, MAdCAM-1, hemoglobin

Abbreviations:
UC: ulcerative colitis
VDZ: vedolizumab
TNF: tumor necrosis factor
IL: interleukin
sMAdCAM-1: soluble mucosal addressin cell adhesion molecule 1
CAI: clinical activity index
VCAM-1: vascular cell adhesion molecule 1
Hb: hemoglobin

Received: September 15, 2023; accepted: December 8, 2023
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CRP: C-reactive protein.

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## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease that mainly affects the colonic mucosa and is characterized by symptoms such as mucous and bloody stool, as well as abdominal pain.[1] These symptoms impair patients' quality of life (QOL) during the active phase of the disease.[2] In comparison with Western countries, the prevalence of UC in Japan has been low but has steadily increased in recent decades.[3,4] As there is currently no known cure for UC, the goals of pharmacotherapy are to alleviate symptoms during the clinically active phase of the disease, maintain QOL by preventing recurrence during the remission phase, prevent carcinogenesis, and avoid surgery. To this end, a treat-to-target strategy with short- or mid-term therapeutic goals has been proposed in recent years (STRIDE-II).[5] With the recent development of tumor necrosis factors alpha (TNFα) antagonists, vedolizumab (VDZ), interleukin (IL)-12/23 inhibitors, and Janus kinase inhibitors,[6-9] there are now more treatment options for UC. Although they have improved the prognosis of UC, challenges remain, including a lack of primary response in some patients and secondary loss of response to treatment over time.[10-12]

VDZ binds to α4β7 integrin expressed on lymphocyte surface, inhibits binding to mucosal addressin cell adhesion molecule 1 (MAdCAM-1)—a ligand for α4β7 expressed on high endothelial venules in gut-associated lymphoid tissue—and prevents lymphocytes from reaching intestinal tissue, thereby inhibiting inflammation.[13,14] The GEMINI trials demonstrated the efficacy of VDZ in inducing and maintaining remission in patients with moderate-to-severe UC who had not or had previously used TNFα antagonists. In randomized controlled trials and real-world practice, the response rate to VDZ in the induction phase has been reported to range from 33.8% to 53.5%.[7,15-17] A systematic review of VDZ for UC reported no statistically significant difference between VDZ and placebo in the incidence of adverse events, including serious ones; serious clostridial infections and sepsis have been reported only rarely.[18] Therefore, VDZ has a good safety profile in terms of infusion-reaction and the incidence of malignancy.[19]

With the increasing number of treatment options, the future challenge for UC treatment lies in establishing personalized treatment strategies, wherein the optimal treatment is selected on an individual basis. However, although some studies and reviews have reported on the treatment response to each therapeutic agent,[20-23] data on predictors of treatment response remain insufficient to establish personalized treatment strategies. Therefore, this study aimed to investigate the real-world effectiveness of VDZ in adult patients with UC and explore factors involved in predicting treatment response.

## METHODS

*Study design*

This single-center, single-arm, prospective observational study included patients with clinically active UC who received VDZ at Nagoya University Hospital between November 2018 and June 2020. The inclusion criteria were as follows: ulcerative colitis diagnosed according to established diagnostic criteria[24]; diagnosed at least 6 months prior to VDZ administration; age 15 years or older; and clinical activity of at least 4 points according to the Lichtiger clinical activity index (CAI).[25,26] VDZ was administered intravenously at 0, 2, 6 weeks, and at 8-week intervals thereafter

at a dose of 300 mg. This study protocol was reviewed and approved by the Ethics Committee of Nagoya University Hospital (approval number [2015-0466]) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients.

*Data collection*

The following information about patients was collected: patients' characteristics, epidemiological information, existing treatment, clinical activity (CAI score), endoscopic score (Ulcerative Colitis Endoscopic Index of Severity [UCEIS]),[27] and blood test data (white blood cell, hemoglobin (Hb), platelet, C-reactive protein (CRP), albumin, erythrocyte sedimentation rate at week 0 (baseline). Serum concentration of TNFα, interferon (IFN) gamma, IL-4, IL-6, IL-10, IL-17, soluble MAdCAM-1 (sMAdCAM-1), and soluble vascular cell adhesion molecule 1 (sVCAM-1) were measured from blood samples by enzyme-linked immunosorbent assay, which was performed using a Quantikine ELISA kit (R and D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Quantitative polymerase chain reaction (qPCR) was performed using TaqManGene Expression Assays (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. Clinical activity at 6 and 14 weeks was assessed based on CAI.

*Outcome measure*

A decrease in CAI score of ≤3 points from baseline was defined as clinical remission. The primary endpoint was the rate of clinical remission at 6 and 14 weeks of VDZ treatment. Secondary endpoints included factors correlated with clinical remission among the following: clinical characteristics of patients at baseline, blood test results, endoscopic score (UCEIS), various serum cytokines in peripheral blood samples, and cytokine-related mRNA expression in the colonic mucosa.

*Statistical analyses*

For data analysis, we used the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA). The Mann–Whitney U test or chi-squared test was performed to compare patients' characteristics in remission and non-remission groups. Statistical significance was set at $P < 0.05$.

## RESULTS

*Patient characteristics*

Table 1 shows patients' characteristics. There were 26 patients, with a median age of 48 years (19–77) at the start of VDZ treatment and a median disease duration of 5.2 years (1.0–31.0). Thirteen patients (50%) had been previously treated with TNFα antagonists; 10 patients (38.5%) had been exposed to one TNFα antagonist, while the other 3 (11.5%) patients had been exposed to two TNFα antagonists. Twenty patients (77.0%) were concomitantly treated with 5-aminosalicylic acid, fourteen (53.8%) with steroids, and eight with immunosuppressants (6-mercaptopurine/azathioprine). The median CAI was 6 (4–14), the median UCEIS was 4 (3–7), and the median CRP was 0.22 mg/dL (0.02–7.98).

**Table 1** Patient characteristics (n=26)

| | |
|---|---|
| Age, median (range), y | 48 (19–77) |
| Male, n (%) | 19 (73.1) |
| Disease duration of UC, median (range), y | 5.2 (1.0–31.0) |
| CAI score, median (range) | 6 (4–14) |
| UCEIS, median (range) | 4 (3–7) |
| CRP, median (range), mg/dL | 0.22 (0.02–7.98) |
| Disease type, n (%) | |
| Pancolitis | 19 (73.1) |
| Left-sided colitis | 7 (26.9) |
| Proctitis | 0 (0) |
| Steroid, n (%) | |
| Refractory | 7 (27.0) |
| Dependency | 11 (42.3) |
| Concomitant medication for UC, n (%) | |
| 5-ASA | 20 (77.0) |
| Steroids | 14 (53.8) |
| Immunosuppressants | 8 (30.8) |
| Prior TNFα antagonists therapy, n (%) | 13 (50) |
| Prior failure of TNFα antagonists, n (%) | |
| Inadequate response | 8 (61.5) |
| Loss of response | 3 (23.1) |
| Intolerance | 2 (15.4) |

UC: ulcerative colitis
CAI: Clinical Activity Index
UCEIS: Ulcerative Colitis Endoscopic Index of Severity
CRP: C-reactive protein
5-ASA: 5-aminosalicylic acid
TNFα: tumor necrosis factors alpha

*Efficacy of VDZ*

Clinical remission at 6 weeks of treatment occurred in 9 (35%) of 26 patients. One patient discontinued treatment due to an adverse event, and four patients discontinued treatment due to primary non-response. At 14 weeks, clinical remission was observed in 11 patients (42%) (Figure 1A).

Fourteen patients were receiving concomitant steroid treatment at the beginning of treatment. Nine (35%) were in steroid-free remission after 6 weeks of treatment, and 10 (38%) were in steroid-free remission after 14 weeks of treatment.

At 6 weeks, 4 (31%) of 13 patients previously treated with TNFα antagonists and 5 (38%) of 13 TNFα antagonist-naïve patients achieved clinical remission. At 14 weeks, clinical remission was observed in 6 (46%) patients previously treated with TNFα antagonists and 5 (38%) TNFα antagonist-naïve patients (Figure 1B).

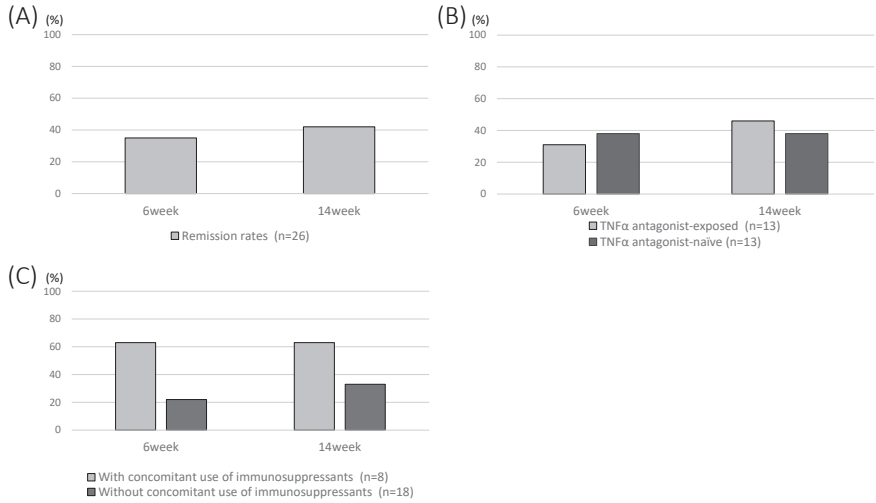


**Fig. 1** Clinical remission rates following VDZ treatment

**Fig. 1A:** Clinical remission rates after 6 and 14 weeks of VDZ treatment.

**Fig. 1B:** Clinical remission rates after 6 and 14 weeks of treatment in patients with and without prior exposure to TNFα antagonist.

**Fig. 1C:** Clinical remission rates after 6 and 14 weeks of treatment in patients with and without concomitant use of immunosuppressant.

VDZ: vedolizumab

TNF: tumor necrosis factor

Furthermore, clinical remission was observed in 5 (63%) of 8 patients with concomitant use of immunosuppressants and 4 (22%) of 18 patients without concomitant use of immunosuppressants. At 14 weeks, 5 (63%) patients with concomitant use of immunosuppressants and 6 (33%) patients without concomitant use of immunosuppressants achieved clinical remission (Figure 1C).

*Comparison of patients' baseline characteristics, blood test results, and endoscopic findings in remission and non-remission groups*

Comparison of patients' characteristics between the remission and non-remission groups after 6 weeks and 14 weeks of treatment showed no significant differences pertaining to age, sex, duration of disease, the extent of disease, steroid resistance, or prior treatment with biological agents.

Blood test results, after 6 weeks, showed no significant intergroup differences in white blood cells (8100 /μL vs 7000 /μL; P = 0.443), albumin (3.8 g/dL vs 3.7 g/dL; P = 0.563), Hb (14.0 g/dL vs 11.8 g/dL; P = 0.178), platelet (276 $10^3$/μL vs 315 $10^3$/μL; P = 0.397), CRP (0.44 mg/dL vs 0.16 mg/dL; P = 0.199), or erythrocyte sedimentation rate (22.0 mm vs 18.0 mm; P = 0.535). Blood test results, after 14 weeks, showed no significant intergroup differences in white blood cells (7600 /μL vs 6200 /μL; P = 0.124), albumin (4.0 g/dL vs 3.5 g/dL; P = 0.158), platelet (296 $10^3$/μL vs 280 $10^3$/μL; P = 0.323), CRP (0.16 mg/dL vs 0.43 mg/dL; P = 0.475), or erythrocyte sedimentation rate (10.0 mm vs 26.0 mm; P = 0.323), whereas Hb was significantly higher in the remission group (14.0 g/dL vs 11.0 g/dL; P = 0.029).

There were no significant differences in CAI (6 vs 7; P = 0.543) and endoscopic score (4 vs 4; P = 0.526) after 6 weeks. There were also no significant differences in CAI (6 vs 8; P = 0.509) and endoscopic score (4 vs 4; P = 0.545) after 14 weeks (Tables 2, 3).

**Table 2** Pre-treatment predictors of response in the remission and non-remission groups at 6 weeks

| | Remission group (n=9) | Non-remission group (n=17) | P-value |
|---|---|---|---|
| Age, median (range), y | 48 (21–73) | 49 (19–77) | 0.526 |
| Sex (male/female) | 8/1 | 11/6 | 0.329 |
| Disease duration of UC, median (range), y | 5.2 (0.5–31.0) | 4.0 (1.0–41.6) | 0.529 |
| Pancolitis, n (%) | 5 (56) | 14 (83) | 0.281 |
| Steroid resistance, n (%) | 3 (33) | 8 (47) | 0.427 |
| Prior use of TNFα antagonists: none, n (%) | 5 (56) | 8 (47) | 0.598 |
| 1 agent, n (%) | 3 (33) | 7 (41) | 0.522 |
| 2 agents, n (%) | 1 (11) | 2 (12) | 0.519 |
| WBC, median (range), /μL | 8100 (5500–19500) | 7000 (3300–12200) | 0.443 |
| Hb, median (range), g/dL | 14.0 (9.6–14.5) | 11.8 (8.7–17.4) | 0.178 |
| Alb, median (range), g/dL | 3.8 (2.5–4.2) | 3.7 (2.1–4.6) | 0.563 |
| Plt, median (range), $10^3$/μL | 276 (172–522) | 315 (122–549) | 0.397 |
| CRP, median (range), mg/dL | 0.44 (0.02–7.98) | 0.16 (0–3.93) | 0.199 |
| ESR per hour, median (range), mm | 22.0 (9–63) | 18.0 (2–70) | 0.535 |
| CAI score, median (range) | 6 (4–14) | 7 (4–13) | 0.543 |
| UCEIS, median (range) | 4 (3–7) | 4 (3–6) | 0.526 |

UC: ulcerative colitis
TNFα: tumor necrosis factors alpha
WBC: white blood cell
Hb: hemoglobin
Alb: albumin
Plt: platelet
CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
CAI: Clinical Activity Index
UCEIS: Ulcerative Colitis Endoscopic Index of Severity

**Table 3** Pre-treatment predictors of response in the remission and non-remission groups at 14 weeks

| | Remission group (n=11) | Non-remission group (n=15) | P-value |
|---|---|---|---|
| Age, median (range), y | 50 (21–73) | 45 (19–77) | 0.460 |
| Sex (male/female) | 8/3 | 11/4 | 0.566 |
| Disease duration of UC, median (range), y | 9.6 (2.3–31.0) | 4.0 (0.5–41.6) | 0.197 |
| Pancolitis (n, %) | 8 (73) | 11 (73) | 0.566 |
| Steroid resistance (n, %) | 5 (45) | 6 (40) | 0.545 |
| Prior use of TNFα antagonists: none (n, %) | 5 (45) | 8 (53) | 0.534 |
| 1 agent (n, %) | 4 (36) | 6 (40) | 0.553 |
| 2 agents (n, %) | 2 (18) | 1 (7) | 0.519 |
| WBC, median (range), /μL | 7600 (7000–19500) | 6200 (3300–12200) | 0.124 |

| | | | |
|---|---|---|---|
| Hb, median (range), g/dL | 14.0 (9–17.4) | 11.0 (8.7–14.5) | 0.029 |
| Alb, median (range), g/dL | 4.0 (2.9–4.4) | 3.5 (2.1–4.6) | 0.158 |
| Plt, median (range), $10^3/\mu L$ | 296 (223–549) | 280 (122–465) | 0.323 |
| CRP, median (range), mg/dL | 0.16 (0.02–5.41) | 0.43 (0–7.98) | 0.475 |
| ESR per hour, median (range), mm | 10.0 (2–60) | 26.0 (4–70) | 0.323 |
| CAI score, median (range) | 6 (4–11) | 8 (4–14) | 0.509 |
| UCEIS, median (range) | 4 (4–7) | 4 (3–6) | 0.545 |

UC: ulcerative colitis
TNFα: tumor necrosis factors alpha
WBC: white blood cell
Hb: hemoglobin
Alb: albumin
Plt: platelet
CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
CAI: Clinical Activity Index
UCEIS: Ulcerative Colitis Endoscopic Index of Severity

*Comparison of colonic mucosal cytokine-related mRNA expression and serum cytokine concentrations in remission and non-remission groups*

After 6 weeks of treatment, the ratios of baseline mRNA expression in colonic mucosal tissue to GAPDH were compared between the remission and non-remission groups for the following cytokines: TNFα (0.81 [0.47–4.29] vs 1.39 [0.10–4.47]; P=0.236), IFNγ (1.77 [0.46–13.2] vs 3.50 [0.67–18.5]; P=0.368), IL-4 (2.58 [0.91–13.5] vs 3.97 [0.72–19.3]; P=0.527), IL-6 (10.1 [0.64–98.4] vs 15.3 [0.78–83.9]; P=0.521), IL-10 (1.17 [0.22–4.35] vs 1.39 [0.20–7.16]; P=0.529), IL-17 (0.77 [0.18–2.93] vs 1.41 [0.04–7.89]; P=0.346), MAdCAM-1 (1.39 [0.19–3.94] vs 2.25 [0.05–7.26]; P=0.510) VCAM-1 (0.15 [0.09–2.48] vs 0.42 [0.00–2.28]; P=0.362). None of these showed a statistically significant intergroup difference.

Similarly, after 14 weeks of treatment, the ratios of baseline mRNA expression to GAPDH were compared between the remission and non-remission groups for the following cytokines, with no statistically significant differences: TNFα (1.21 [0.10–9.71] vs 1.32 [0.22–4.28]; P=0.566), IFNγ (11.5 [0.46–18.5] vs 2.89 [0.54–9.31]; P=0.393), IL-4 (5.88 [1.16–19.3] vs 3.65 [0.72–11.6]; P=0.260), IL-6 (24.4 [0.64–333] vs 15.3 [0.78–83.9]; P=0.368), IL-10 (1.75 [0.20–6.72] vs 0.91 [0.22–2.85]; P=0.152), IL-17 (1.26 [0.04–15.2] vs 1.16 [0.07–4.63]; P=0.517), MAdCAM-1 (1.96 [0.05–6.91] vs 1.68 [0.11–7.26]; P=0.513) VCAM-1 (0.35 [0.01–2.48] vs 0.30 [0.08–1.75]; P=0.542).

Baseline serum cytokine levels between the remission and non-remission groups at 6 weeks were compared, but there were no significant differences in TNFα (5.57 [0.21–28.6] vs19.0 [0.21–70.6]; P=0.504), IFNγ (2.09 [0.29–6.10] vs 1.73 [0.29–9.43]; P=0.575), IL-4 (5.40 [5.40–13.4] vs 5.93 [4.87–12.2]; P=0.549), IL-6 (2.07 [0.00–31.6] vs 3.03 [0.10–16.6]; P=0.558), IL-10 (8.46 [4.12–12.1] vs 7.30 [4.99–17.5]; P=0.551), IL-17 (10.3 [9.27–11.3] vs 11.3 [9.27–17.7]; P=0.130), sMAdCAM-1 (768 [415–1019] vs 689 [287–917]; P=0.507), or sVCAM-1 (211 [182–249] vs 200 [106–247]; P=0.092).

Comparison of baseline serum cytokine concentrations between the remission and non-remission groups at 14 weeks revealed a significant difference in sMAdCAM-1 (806 [415–1019] vs 659 [287–917]; P=0.033), but there were no significant differences in TNFα (5.34 [0.21–70.6] vs11.8 [1.12–44.3]; P=0.521), IFNγ (1.72 [0.29–3.90] vs 2.08 [0.29–9.43]; P=0.541), IL-4

(5.40 [5.40–10.4] vs 5.93 [5.40–13.4]; P=0.524), IL-6 (1.71 [0.00–4.81] vs 2.78 [0.88–5.23]; P=0.361), IL-10 (6.92 [4.12–9.86] vs 7.69 [4.99–14.5]; P=0.182), IL-17 (10.4 [9.27–14.1] vs 11.0 [9.96–17.7]; P=0.140), or sVCAM-1 (206 [160–245] vs 202 [106–249]; P=0.374) (Figures 2, 3).

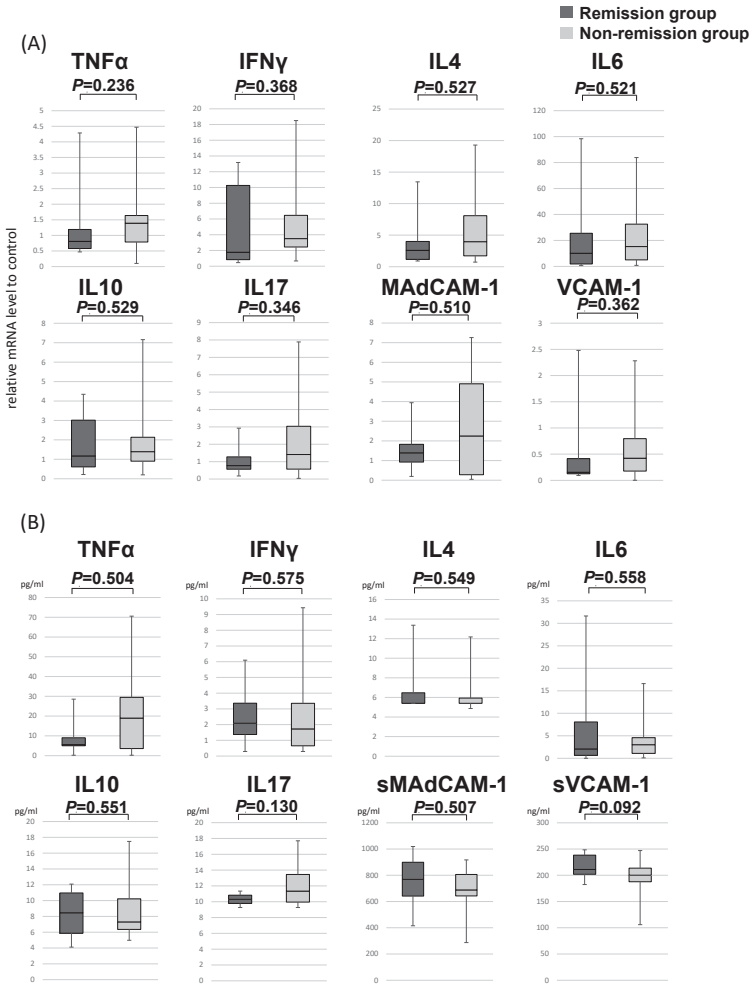


**Fig. 2** Molecular characteristics of the remission and non-remission groups at 6 weeks

The horizontal lines represent median values; the lower and upper boundaries of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the highest and lowest points.

**Fig. 2A:** Comparison of colonic mucosal cytokine-related mRNA expression between the remission and non-remission groups.

**Fig. 2B:** Comparison of serum cytokine concentrations between the remission and non-remission groups.

TNF: tumor necrosis factor

IFN: interferon

IL: interleukin

MAdCAM-1: mucosal addressin cell adhesion molecule 1

VCAM-1: vascular cell adhesion molecule 1

sMAdCAM-1: soluble mucosal addressin cell adhesion molecule 1

sVCAM-1: soluble vascular cell adhesion molecule 1

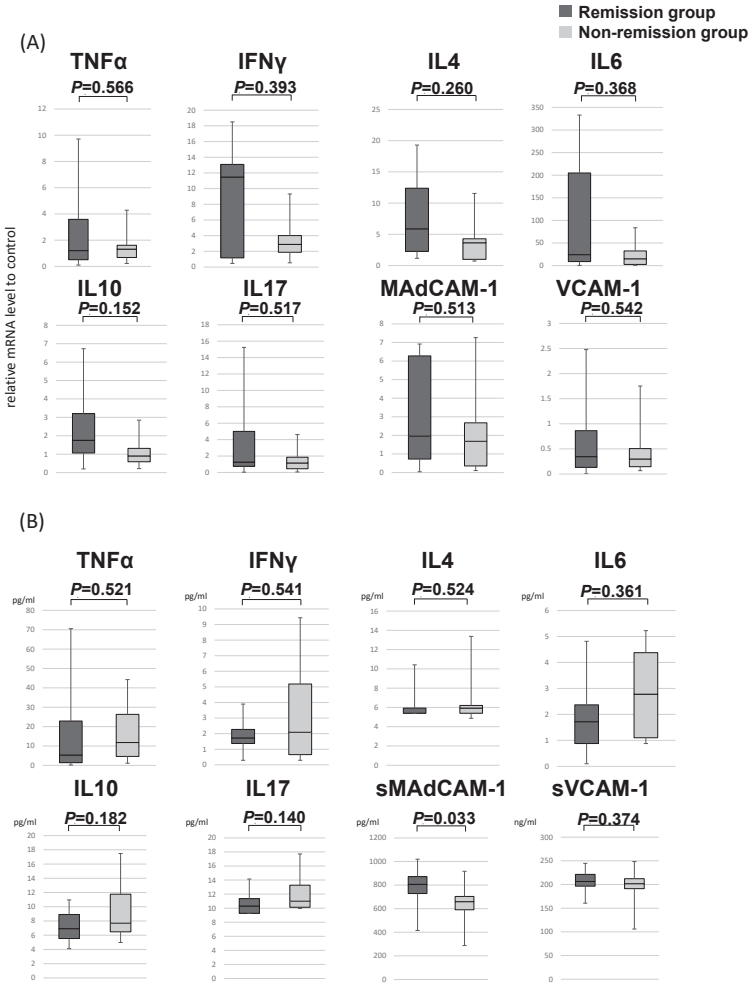


**Fig. 3** Molecular characteristics of the remission and non-remission groups at 14 weeks

The horizontal lines represent median values; the lower and upper boundaries of the boxes represent the 25th and 75th percentiles, respectively; the whiskers represent the highest and lowest points.

**Fig. 3A:** Comparison of colonic mucosal cytokine-related mRNA expression between the remission and non-remission groups.

**Fig. 3B:** Comparison of serum cytokine concentrations between the remission and non-remission groups.

TNF: tumor necrosis factor
IFN: interferon
IL: interleukin
MAdCAM-1: mucosal addressin cell adhesion molecule 1
VCAM-1: vascular cell adhesion molecule 1
sMAdCAM-1: soluble mucosal addressin cell adhesion molecule 1
sVCAM-1: soluble vascular cell adhesion molecule 1

*Cutoffs for Hb and sMAdCAM-1*

Next, we examined how accurately Hb and sMAdCAM-1 predicted clinical response to treatment. The area under the receiver operating characteristic curve value was 0.770 for Hb and 0.764 for sMAdCAM-1. At the cutoff value of 11.5 g/dL for Hb, the sensitivity was 90.9%, the

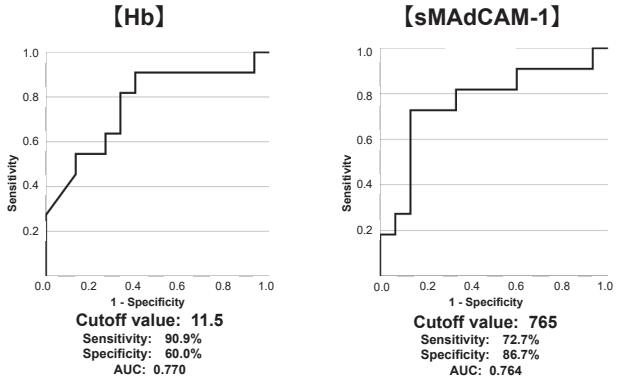


**Fig. 4** ROC curves for Hb and sMAdCAM-1
ROC: receiver operating characteristics
Hb: hemoglobin
sMAdCAM-1: soluble mucosal addressin cell adhesion molecule 1
AUC: area under the curve

specificity was 60.0%, the positive predictive value was 62.5%, and the negative predictive value was 90.0%. At the cutoff value of 765 pg/mL for sMAdCAM-1, the sensitivity was 72.7%, the specificity was 86.7%, the positive predictive value was 80.0%, and the negative predictive value was 81.3% (Figure 4). At Hb and sMAdCAM-1 concentrations exceeding these cutoff values, treatment response was predicted with a sensitivity of 88.9% and specificity of 81.3%.

*Analysis of background factors associated with efficacy*

Univariate analysis of factors associated with efficacy showed that Hb ≥ 11.5 g/dL (OR, 15.0; 95% CI 1.50 to 149; P=0.014) and sMAdCAM-1 ≥ 765 pg/mL (OR, 17.3; 95% CI 2.36

**Table 4** Background factors associated with the efficacy of vedolizumab

| | P-value | OR | (95% CI) |
|---|---|---|---|
| Male sex | 1.000 | 0.97 | (0.17–5.59) |
| Pancolitis | 0.683 | 0.64 | (0.12–3.41) |
| Prior exposure to TNFα antagonists | 0.691 | 1.37 | (0.29–6.53) |
| Concomitant use of immunosuppressants | 0.218 | 3.33 | (0.59–18.89) |
| CAI (≥11) | 0.356 | 0.28 | (0.03–2.89) |
| Hb, g/dL (≥11.5) | 0.014 | 15.0 | (1.50–149) |
| CRP, mg/dL (≥0.3) | 0.394 | 0.50 | (0.10–2.46) |
| Alb, g/dL (≥3.5) | 0.178 | 6.67 | (0.67–66.5) |
| sMAdCAM-1, pg/mL (≥765) | 0.004 | 17.3 | (2.36–127) |

OR: odds ratio
CI: confidence interval
CAI: Clinical Activity Index
Hb: hemoglobin
CRP: C-reactive protein
Alb: albumin
sMAdCAM-1: soluble mucosal addressin cell adhesion molecule 1

to 127; P=0.004) were significant factors, whereas other factors, such as sex, extent of disease, prior use of TNFα antagonists, concomitant use of immunosuppressants, CAI, CRP, and Alb, were not (Table 4).

## DISCUSSION

In the GEMINI-1 trial, the induction-phase efficacy endpoint was evaluated at 6 weeks. However, it is possible that VDZ administration as induction therapy was not maximally effective during the 6-week treatment period, suggesting that a longer induction phase may be more effective.[7] Therefore, in the phase III trial conducted in Japan, efficacy was evaluated at 10 weeks of treatment. In this study, the remission rate at 6 weeks was 35%, whereas the remission rate at 14 weeks was 42%. The phase III trial conducted in Japan had a mean age of 42.3 years (SD ± 14.4) and a mean disease duration of 7.2 years (SD ± 6.2) at the start of the VDZ treatment. Eighty-five patients (51.8%) had been previously treated with TNFα antagonists, 145 patients (88.4%) were concomitantly treated with 5-aminosalicylic acid, 59 patients (18.9%) with steroids only, and 21 patients (12.8%) with steroids and immunosuppressants. The clinical score (Mayo score) was 8.3 (SD ± 1.5), and a CRP level ≥3 was observed in 88 (53.7%) patients. The current study seemed to be slightly less severe regarding the clinical score and presented slightly lower CRP levels. Background factors reported to be associated with the efficacy of VDZ include the absence of previous exposure to TNFα antagonists, moderate or lower endoscopic activity, and absence of a decrease in serum albumin concentration.[23,28] Furthermore, higher levels of inflammation and clinical severity (CRP ≥2 mg/L, Mayo score ≥9, etc) have been linked to lower efficacy.[22,29] In this study, we established that Hb ≥ 11.5 g/dL was a predictor of potential VDZ efficacy. Conversely, low Hb has been reported as a predictor of poor efficacy in treatment with TNFα antagonists.[30,31] Hb is one of the key parameters for UC in the Truelove–Witts criteria as well.[31] Low Hb has been linked to higher disease severity, poor prognosis, and the risk of acute exacerbation.[32] Low Hb in UC is attributed to intestinal bleeding resulting from mucosal inflammation and inhibition of erythropoiesis by cytokines or hepcidin associated with chronic inflammation, decreasing iron absorption and retaining iron in the reticular-endothelial system.[33] This suggests that low Hb level may result from persistent chronic inflammation in UC, which may correlate with the efficacy of VDZ. No difference in treatment efficacy depending on prior exposure to TNFα antagonists was observed in this study. The results of previous randomized controlled trials indicate that TNFα antagonists, VDZ, and ustekinumab all have higher efficacy when used in patients naïve to TNF antagonists.[11,34] In the GEMINI-1 trial, VDZ also showed greater efficacy in patients naïve to TNFα antagonists in comparison to those with prior exposure to TNFα antagonists.[35] The diminishing efficacy of the second and subsequent uses of TNFα antagonists may be attributed to the following causes: the inflammation is primarily caused by mechanisms other than TNFα; poor pharmacokinetics; immunogenicity resulting from the first exposure to a TNFα antagonists that may cause sensitization to other TNFα antagonists.[36] Furthermore, the reason why VDZ and ustekinumab had better efficacy in patients naïve to TNFα antagonists is that patients with prior exposure to TNFα antagonists generally have longer disease duration, chronic intestinal inflammation, and a history of extraintestinal symptoms compared with naïve patients.[37] No difference in treatment efficacy depending on prior exposure to TNFα antagonists was observed in this study, which could be attributed to the small sample size. There was no difference in remission rates with or without concomitant use of immunosuppressants. Combination therapy with infliximab, a TNFα antagonist, and azathioprine, an immunosuppressant, has been reported to have higher efficacy than monotherapy with either agent.[38] This is

supported by the higher trough concentrations of TNFα antagonists measured in patients who received combination therapy, as well as the possibility that immunosuppressants reduce the rate of antibody formation.[39] However, the efficacy of combination therapy with VDZ and ustekinumab has not yet been established, and some studies have found no significant difference in clinical remission or endoscopic response rate with the combination of immunosuppressants.[40,41] A similar trend was observed in the present study.

High serum sMAdCAM-1 level at baseline was found to be a predictor of treatment efficacy in this study. To the best of our knowledge, this is the first study to establish baseline serum sMAdCAM-1 level as a predictor of treatment efficacy. Since VDZ specifically inhibits α4β7 from binding to MAdCAM-1, it is possible that MAdCAM-1 is predominantly involved in lymphocyte migration in the intestinal mucosa in cases with high serum MAdCAM-1 levels, and VDZ may be more effective in such cases. Furthermore, lymphocyte migration to the colonic mucosa involves factors other than MAdCAM-1, such as VCAM-1 and intercellular adhesion molecule 1.[42] VDZ does not inhibit α4β1 from binding to VCAM-1, which is associated with inflammation in the colon, nor does it inhibit β2 integrin-mediated leukocyte adhesion to transmembrane intercellular adhesion molecule 1 in the gut.[13,43] Therefore, VCAM-1 and intercellular adhesion molecule 1 may be predominantly involved in lymphocyte migration in patients without high MAdCAM-1 expression, and inhibition of α4β7 alone may be insufficient for these patients.[44] In a previous study, VDZ responders had significantly higher sMAdCAM-1 levels after the induction phase than non-responders but not soluble intercellular adhesion molecule 1 or sVCAM-1 levels.[45] Our analysis showed that baseline sMAdCAM-1 levels were correlated with treatment response, which is consistent with previous research findings, although the timing of measurement was different.

By contrast, the MAdCAM-1 mRNA expression in colon tissue did not show a clear correlation with treatment response in this study. MAdCAM-1 has been reported to be highly expressed in the inflamed mucosa surrounding active ulcers, whereas the MAdCAM-1 expression is rather decreased in the area near the ulcer base.[46] This suggests that even if there is MAdCAM-1-dependent inflammation, the mucosal expression of MAdCAM-1 is heterogeneous and may vary depending on the site of tissue collection. Therefore, there was no uniformity in mucosal collection sites in this study, which may explain why MAdCAM-1 mRNA expression was not found to be correlated with treatment response.

The present study has several limitations. This was a single-center study with small sample sizes per stratum. Hb, a predictor of treatment response, may also be a confounding factor with severity; nonetheless, the small number of cases made it inappropriate for multivariate analysis. In addition, this was conducted at a tertiary care center, which may involve bias related to the selection of referred patients. In addition, the dosing intervals of vedolizumab were 6 and 14 weeks; therefore, a direct comparison with the 10-week intervals in previous clinical trials was not possible. A larger, multicenter study may be required for further investigation.

With advances in the development of biologic agents for patients with UC, therapeutic strategies that determine the most appropriate drug at any given time will be critical. This is expected to improve treatment response rates and influence the duration of remission. Accumulation of evidence on predictors of treatment response is critical for establishing personalized treatment. The present study established that Hb levels of 11.5 g/dL or higher and sMAdCAM-1 levels of 765 pg/mL or higher predicted treatment response with a sensitivity of 88.9% and specificity of 81.3%. More research is needed to identify factors that can further increase the prognostic accuracy.

## CONCLUSION

VDZ is an effective therapy for UC. Hb and serum sMAdCAM-1 levels are factors correlated with the therapeutic efficacy of VDZ. The findings of the present study may aid clinicians in selecting appropriate treatment options for patients with UC. As the number of treatment options for UC increases, it is desirable to accumulate more research findings to establish personalized treatment strategies, where the optimal treatment is selected on an individual basis.

## ACKNOWLEDGMENTS

*Author contributions*

K.G. and S.T.: conception and design of the study; K.G., S.T., M.K., I.E., H.T., M.Y., and F.K.: data collection; K.G., S.T., N.M., Y.T., U.K., I.T. and Y.K.: analyzed and interpreted the data; K.G. and S.T.: drafted the manuscript; I.T.: provided critical revision of the article for important intellectual content; K.H.: gave final approval of the article.

*Conflict of interest and financial disclosures*

The authors received no funding for this study. The authors have no conflicts of interest to declare.

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