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Vedolizumab–steroid combination therapy improves long-term prognosis in patients with ulcerative colitis

Yosuke Yamada^{1,2}, Natsuki Ishida^{2*}, Tomohiro Takebe², Kenichi Takahashi², Yusuke Asai², Satoshi Tamura², Tomoharu Matsuura³, Ryosuke Takano⁴, Ai Matsuura⁴, Mihoko Yamade², Moriya Iwaizumi³, Yasushi Hamaya², Takanori Yamada⁵, Satoshi Osawa⁵, Yashiro Yoshizawa¹, Yoshisuke Hosoda¹, Yuji Ota⁴, Hiroyuki Hanai⁴ and Ken Sugimoto²

Abstract

Background In real-world clinical settings, the clinical efficacy of vedolizumab (VDZ) in patients with ulcerative colitis (UC) remains unclear. In this study, we aimed to evaluate the efficacy of prednisolone (PSL)–VDZ combination therapy in patients with UC.

Methods Changes in the clinical activity index (CAI), blood test results, and the factors affecting VDZ rate and continuity were investigated. Patients who received at least 20 mg PSL within 1 week of VDZ induction were included in the VDZ + rapid PSL induction (VDZ + rPSL) group, and the remaining were assigned to the non-VDZ + rPSL group. Failure and non-failure in both groups were compared.

Results We conducted a comparative analysis of 38 patients with UC treated with VDZ (VDZ + rPSL, $n = 14$; non-VDZ + rPSL, $n = 24$). The CAI in both groups improved significantly from week 2 to 24 compared with the pretreatment values ($P < 0.01$). Clinical remission and response at week 8 were significantly higher in the VDZ + rPSL group than in the non-VDZ + rPSL group (85.7% vs. 37.5%, $P < 0.01$ and 85.7% vs. 41.7%, $P = 0.02$, respectively). Kaplan–Meier analysis showed a significant difference in the failure-free rate between the two groups (log-rank test, $P = 0.02$). In the VDZ + rPSL group, only C-reactive protein (CRP) levels significantly improved in non-failure at week 2 ($P = 0.04$).

Conclusions VDZ + rPSL induction therapy is beneficial for UC treatment. CRP levels 2 weeks after VDZ induction may influence the continuation rate in the VDZ + rPSL group.

Keywords Ulcerative colitis, Vedolizumab, Steroid, C-reactive protein

*Correspondence:

Natsuki Ishida

ma03006@hama-med.ac.jp

¹Department of Gastroenterology, Seirei Hamamatsu General Hospital, Hamamatsu, Shizuoka, Japan

²First Department of Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

³Department of Laboratory Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

⁴Department of Gastroenterology, Hamamatsu Rosai Hospital, Hamamatsu, Shizuoka, Japan

⁵Department of Endoscopic and Photodynamic Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan



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Background

Ulcerative colitis (UC) is a chronic inflammatory condition that usually follows a remitting-relapsing course [1]. The basic treatment for moderate-to-severe UC is steroids, which have been used to induce remission since Truelove et al. first reported their efficacy in 1955 [2]. However, steroid refractoriness and dependence frequently manifest with steroid-based therapies for UC [1, 3]. Long-term colectomy is a risk factor, especially if rescue therapy during an acute attack is required because of steroid refractoriness [4]. Prolonged steroid administration for managing UC is unfavorable because of its association with immediate and long-term adverse effects [5]. Steroid treatment limitations have made UC treatment difficult, but therapeutic options have expanded in recent years with advances in various types of treatments for UC. Biologics have emerged as promising therapies for patients with UC refractory to conventional medical treatment [6].

Vedolizumab (VDZ) is a humanized monoclonal antibody that selectively antagonizes the $\alpha 4\beta 7$ gastrointestinal integrin receptor and is indicated for treating patients with moderate-to-severe UC and Crohn's disease (CD) [7].

GEMINI 1, a randomized, double-blind, placebo-controlled Phase III trial, was conducted to evaluate the efficacy and safety of VDZ for inducing and maintaining UC remission [8]. In the GEMINI 1 study, the response rate at 6 weeks was significantly higher in the VDZ group (47.1%) than in the placebo group (25.5%; $P < 0.001$). Additionally, the remission rate at 52 weeks was significantly higher in the VDZ group (41.8%) than in the placebo group (15.9%; $P < 0.001$) [8]. Moreover, VERSITY, a direct double-blind Phase III study, was conducted to further assess the efficacy of VDZ in comparison with adalimumab (ADA) [9]. Therein, the remission rates at 52 weeks were 31.3% in the VDZ group and 22.5% in the ADA group, with the VDZ group demonstrating a significantly higher remission rate ($P = 0.006$). The endoscopic mucosal healing rate at 52 weeks was 39.7% in the VDZ group and 27.7% in the ADA group, with the VDZ group showing a significantly higher remission rate than the ADA group ($P < 0.001$) [9].

Although the clinical efficacy of VDZ in patients with UC has been assessed in large-scale trials, adequate data regarding its efficacy in real-world clinical settings are lacking. Specifically, VDZ is not a biological therapy that targets inflammatory cytokines implicated in the pathogenesis of UC; instead, it inhibits lymphocyte migration into tissues to achieve its anti-inflammatory effects. Concern exists for patients with moderate-to-severe UC who may experience delayed onset of therapeutic benefits. We hypothesized that treatment with a combination of VDZ and steroids would reduce UC activity at an early stage

and confer long-term therapeutic benefits. Accordingly, in this study, we evaluated the efficacy of VDZ in combination with steroids across multiple centers, focusing on clinical activity and laboratory test outcomes.

Methods

Patients and study design

This retrospective, multicenter, observational study included patients with UC treated with VDZ at the Seirei Hamamatsu General Hospital, Hamamatsu University School of Medicine, and Hamamatsu Rosai Hospital between August 2018 and October 2023. UC was diagnosed according to established clinical, endoscopic, and histological diagnostic criteria [10]. Patients with inflammatory bowel disease (IBD) who were not diagnosed with UC but were diagnosed with indeterminate colitis or unclassified IBD were excluded. Patients with a clinical activity index (CAI) ≤ 4 were excluded to focus on those with an active disease. To evaluate the efficacy of VDZ therapy, patients receiving ongoing prednisolone (PSL) treatment were also excluded. The primary endpoint of this study was the continuation of treatment with VDZ + rapid PSL (rPSL) induction.

The secondary endpoints were changes in the CAI and laboratory findings at weeks 0, 2, 8, and 24. We defined the VDZ + rPSL group as those receiving at least 20 mg PSL within 1 week of VDZ induction. The remaining patients were assigned to the non-VDZ + rPSL group. We believed that the combination of earlier PSL regimens would enhance the efficacy of VDZ induction therapy.

Disease assessment

We evaluated the clinical disease activity using the CAI according to the report by Rachmilewitz [11]. Clinical remission was defined as a CAI ≤ 4 , whereas clinical response was defined as a decrease of 4 points or 50% in the CAI compared with the baseline. Serum albumin (Alb), hemoglobin (Hb), and C-reactive protein (CRP) levels were measured in each facility's laboratory test department. The endoscopic UC score was evaluated using the Mayo Endoscopic Subscore (MES). The criteria for MES were as follows: 0, normal or inactive disease; 1, mild disease with erythema, decreased vascular pattern, and mild friability; 2, moderate disease with marked erythema, absence of vascular patterns, friability, and erosions; and 3, severe disease with spontaneous bleeding and ulceration [12].

Treatment and follow-up of patients

The enrolled patients visited our hospital regularly, once every 2 weeks for 2 months. Intravenous infusions of 300 mg VDZ were administered on day 1 and at weeks 2 and 6 during the induction phase and every 8 weeks during the maintenance phase. Switching from VDZ to

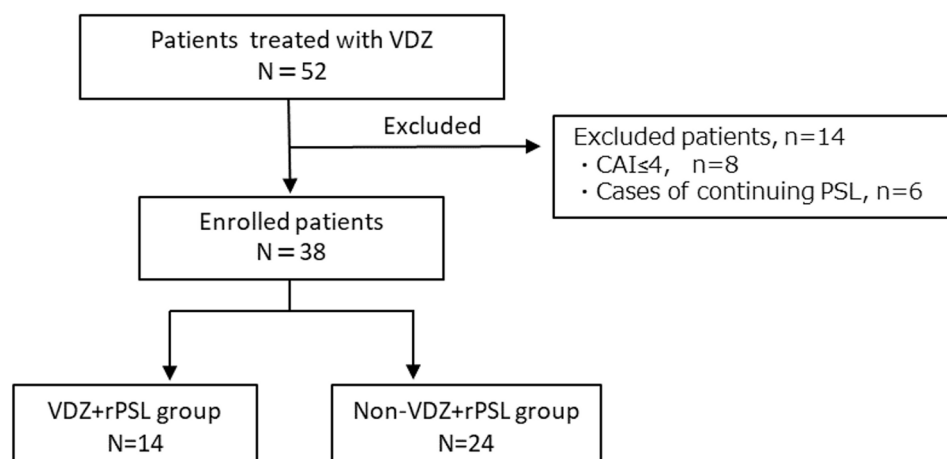


Fig. 1 Study flowchart. VDZ, vedolizumab; CAI, clinical activity index; PSL, prednisolone; rPSL, rapid prednisolone

Table 1 Baseline characteristics

Characteristics at entry		All N=38	VDZ + rPSL group n=14	Non-VDZ + rPSL group n=24	P-value
Age (year), median [IQR]		37.5 [26–53.3]	37.5 [23–43.25]	37.5 [26.75–55]	0.39
Male / Female, n (%)		22 (57.9) / 16 (42.1)	9 (64.3) / 5 (35.7)	13 (54.2) / 11 (45.8)	0.74
Disease duration (year), median [IQR]		7.5 [3–15]	8 [3.25–14.5]	7.5 [3.0–15]	0.82
Disease extent, n (%)	Extensive colitis	29 (76.3)	10 (71.4)	19 (79.2)	0.70
	Left-sided colitis	9 (23.7)	4 (28.6)	5 (20.8)	
CAI (Rachmilewitz index), median [IQR]		7 [6–9]	6.5 [6–7.75]	7 [0.5–9]	0.59
CRP (mg/dL), median [IQR]		0.21 [0.04–1.08]	0.21 [0.14–0.67]	0.20 [0.03–1.19]	0.72
Alb (g/dL), median [IQR]		4 [3.5–4.2]	4.0 [3.55–4.20]	4.0 [3.48–4.20]	0.62
Hb (g/dL), median [IQR]		12.75 [10.7–13.9]	13.25 [11.45–14.15]	12.45 [10.47–13.43]	0.33
MES, n (%)	MES 1	3 (7.9)	1 (7.1)	2 (8.3)	0.13
	MES 2	22 (57.9)	11 (78.6)	11 (45.8)	
	MES 3	13 (34.2)	2 (14.3)	11 (45.8)	
Other medication at entry, n (%)	Oral 5-ASA	27 (71.1)	9 (64.3)	18 (75.0)	0.71
	Suppository steroids	5 (13.2)	2 (14.3)	3 (12.5)	1.00
	Systemic steroids	23 (60.5)	12 (85.7)	11 (45.8)	0.02
	Immunomodulators	11 (28.9)	3 (21.4)	8 (33.3)	0.49
	Oral tacrolimus	3 (7.9)	0 (0.0)	3 (12.5)	0.28

VDZ + rPSL, vedolizumab + rapid prednisolone induction; IQR, interquartile range; CAI, clinical activity index; CRP, C-reactive protein; Alb, albumin; Hb, hemoglobin; MES, Mayo endoscopic subscore; 5-ASA, 5-aminosalicylic acid

another treatment because of an increase in the number of bowel movements, the appearance of bloody stools, and an increase in CAI by ≥ 4 points was defined as failure. Further treatment decisions were left at the discretion of the attending physician. Some laboratory data were missing because some patients did not visit the hospital owing to inconvenience.

Statistical analysis

Statistical analyses were performed using SPSS v24 (IBM Corp., Armonk, NY, USA) and EZR (Saitama Medical Center, Jichii Medical University, Saitama, Japan) software [13]. The Wilcoxon signed-rank test or Fisher's exact test was used to evaluate the differences. Kaplan–Meier analysis with the log-rank test was used to evaluate

the cumulative failure-free rate. Statistical significance was set at $P < 0.05$.

Results

Patient characteristics

The patient selection flowchart is shown in Fig. 1. A total of 38 patients were included in the final analysis (Table 1). The patient backgrounds, including clinical and endoscopic activity, were not significantly different between the VDZ + rPSL and non-VDZ + rPSL groups (Table 1).

Comparison of clinical activity between the VDZ + rPSL and non-VDZ + rPSL groups

The percentage change in the CAI from baseline at the initiation of VDZ was evaluated at weeks 2, 4, 8, and 24 in both groups (Fig. 2). The CAI in both groups improved

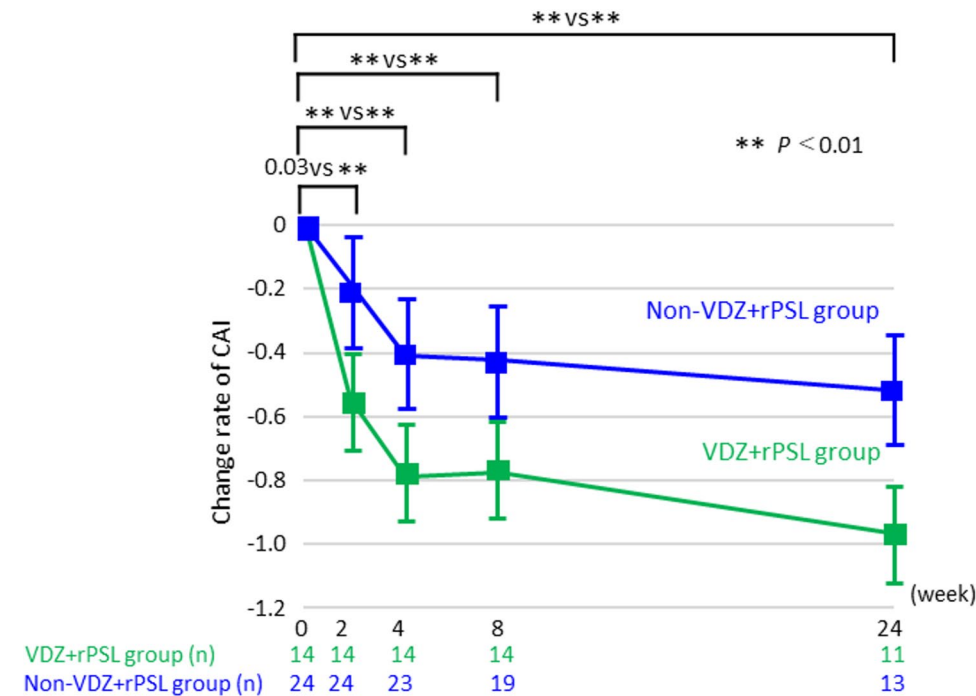


Fig. 2 Changes in CAI after VDZ induction. VDZ, vedolizumab; CAI, clinical activity index; rPSL, rapid prednisolone

significantly from weeks 2 to 24 compared with the pretreatment values ($P < 0.01$). The clinical remission and response at week 2 were significantly higher in the VDZ+rPSL group than in the non-VDZ+rPSL group ($P = 0.04$ for both) (Fig. 3A and B). The clinical remission and response at week 8 were also significantly higher in the VDZ+rPSL group than in the non-VDZ+rPSL group ($P < 0.01$ and $P = 0.02$, respectively; Fig. 3C and D). Kaplan–Meier analysis revealed the VDZ failure-free rates were significantly higher in the VDZ+rPSL group than in the non-VDZ+rPSL group (log-rank test $P = 0.02$) (Fig. 4).

Comparison of laboratory data between the VDZ+rPSL and non-VDZ+rPSL groups

Changes in blood test findings from baseline at the initiation of VDZ were evaluated at weeks 2, 4, 8, and 24 in both groups (Fig. 5). Serum Alb levels improved significantly in the VDZ+rPSL group at week 24 but not in the non-VDZ+rPSL group ($P = 0.03$) (Fig. 5A and B). No significant improvement in Hb levels was observed in either group (Fig. 5C and D). CRP levels significantly improved at week 2 in the VDZ+rPSL group and at week 4 in the non-VDZ+rPSL group ($P = 0.02$ for both) (Fig. 5E and F). Finally, the VDZ+rPSL and non-VDZ+rPSL groups were further divided into the failure and non-failure subgroups, and Alb, Hb, and CRP levels at weeks 0 and 2 were compared (Fig. 6). Alb and Hb levels were not significantly different between weeks 0 and 2 in either group (Fig. 6A–D). No significant difference in CRP level was

observed between weeks 0 and 2 in the non-VDZ+rPSL group; however, in the VDZ+rPSL group, a significant improvement was observed in the non-failure group at week 2 ($P = 0.04$) (Fig. 6E and F).

Discussion

In this study, we examined the efficacy of early combined administration of PSL and VDZ, an intestine selective anti- $\alpha 4\beta 7$ integrin antibody for UC, in a real-world setting. The GEMINI trial demonstrated the beneficial effects of VDZ in treating UC [8, 14]. The basis for treating UC is inducing and maintaining remission, and the GEMINI trial conducted a detailed analysis of these aspects. However, the GEMINI study did not examine the association between steroids and vedolizumab in detail. Given the difficulty of establishing the complex conditions of the GEMINI trial in a clinical setting, we aimed to assess the efficacy of VDZ in real-world clinical settings at participating centers, specifically evaluating its effectiveness in combination with PSL.

In our study, 23 patients (60.5%) received systemic steroids at the start of the VDZ treatment. We compared the efficacy of VDZ and early PSL combination therapy with VDZ alone because we hypothesized that the combination therapy might be more effective in inducing and maintaining remission. Herein, the CAI showed significant improvement in the VDZ+rPSL and non-VDZ+rPSL groups compared with the pretreatment levels, with the enhancement being more pronounced in the VDZ+rPSL group. The clinical remission and response

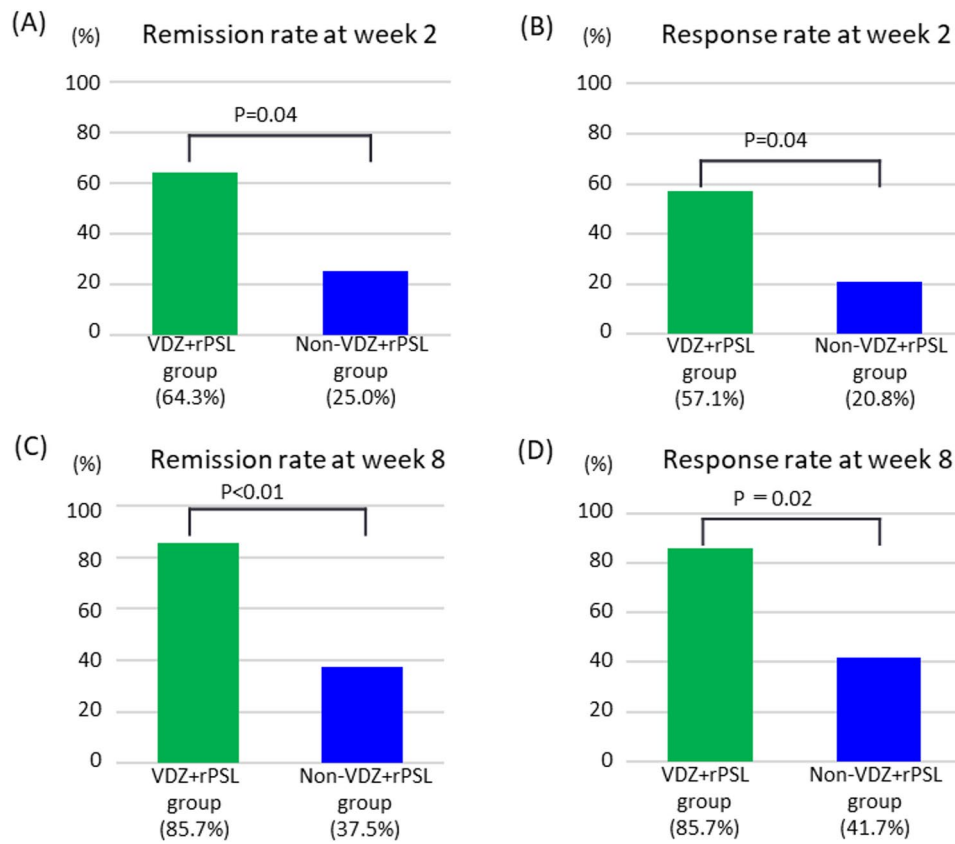


Fig. 3 Comparison of clinical remission and response at weeks 2 and 8. **(A)** Remission rate at week 2; **(B)** Response rate at week 2; **(C)** Remission rate at week 8; and **(D)** Response rate at week 8. VDZ, vedolizumab; rPSL, rapid prednisolone

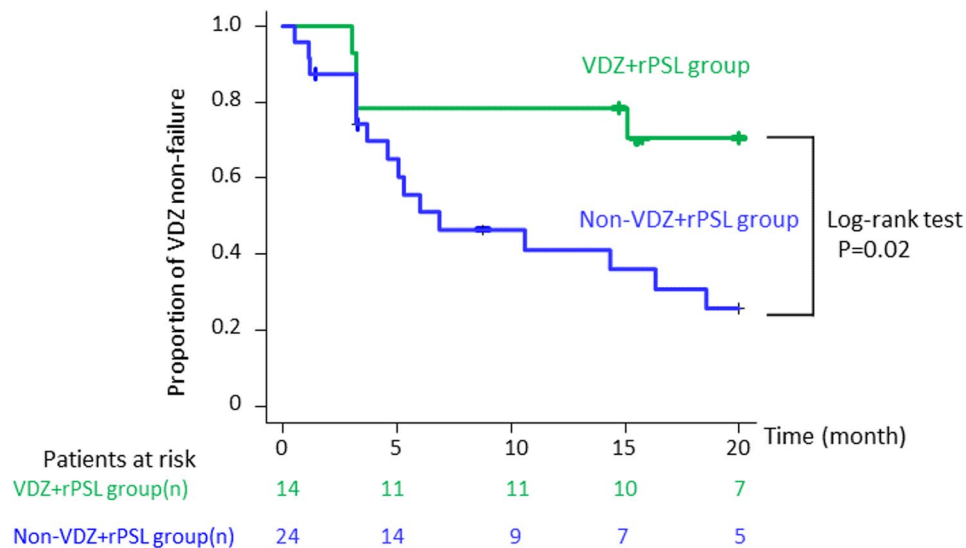


Fig. 4 Comparison of VDZ failure-free rates in the VDZ-rPSL and non-VDZ-rPSL groups. VDZ, vedolizumab; rPSL, rapid prednisolone

rates were higher in the VDZ+rPSL group than in the non-VDZ+rPSL group at weeks 2 and 8. To our knowledge, no study has evaluated the efficacy of VDZ+PSL combination therapy in treating UC. Regarding CD, a previous report indicated that VDZ+PSL combination

therapy effectively induced remission [15]. Sands et al. [15] analyzed patients enrolled in the GEMINI 2 and 3 trials. They observed that in the GEMINI 2 trial, combining VDZ and PSL had a significantly higher clinical remission rate than VDZ alone at week 6 (19.0% vs.

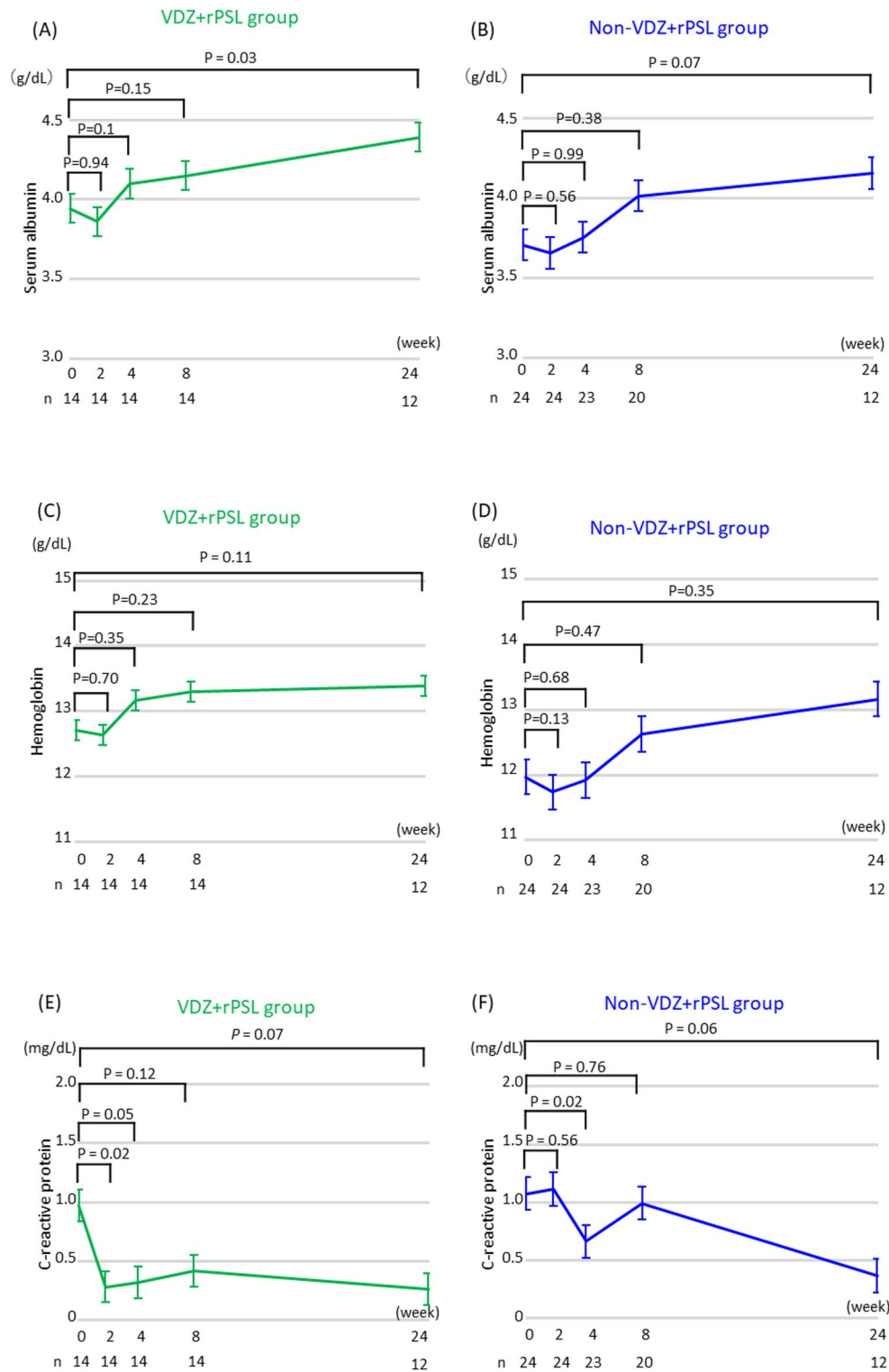


Fig. 5 Comparison of changes in serum albumin (A, B), hemoglobin (C, D), and C-reactive protein (E, F) levels from week 0 to 4 between the VDZ + rPSL and non-VDZ + rPSL groups. VDZ, vedolizumab; rPSL, rapid prednisolone

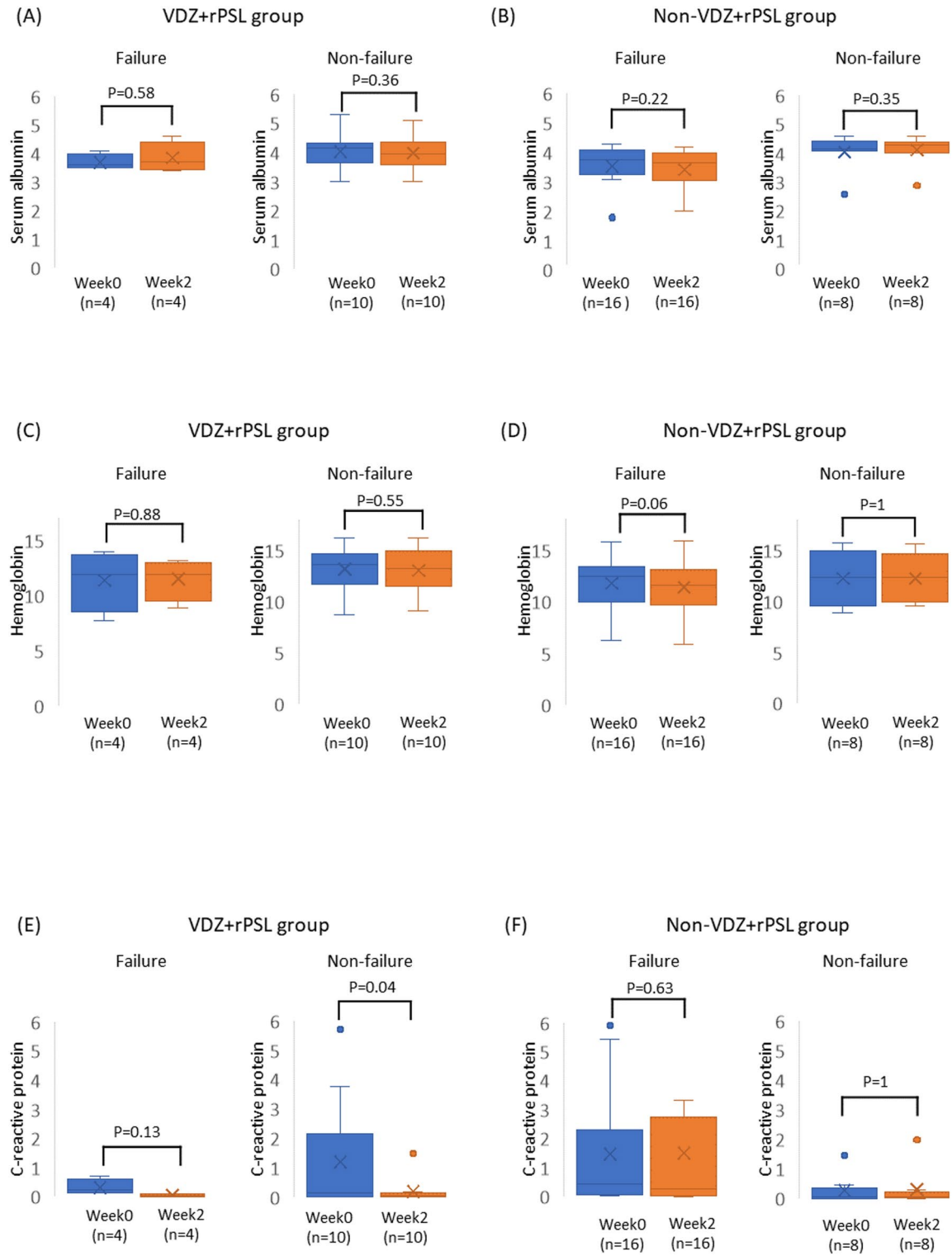


Fig. 6 Comparison of the serum albumin (A, B), hemoglobin (C, D), and C-reactive protein (E, F) levels between the failure and non-failure groups. VDZ, vedolizumab; rPSL, rapid prednisolone

10.9%). In the GEMINI 3 trial, combining VDZ and PSL had a significantly higher clinical remission rate than VDZ alone at week 10 (34.2% vs. 22.7%). In our study, the VDZ+rPSL group showed higher clinical remission and response rates than the non-VDZ+rPSL group at weeks 2 and 8. Therefore, we considered that combining VDZ and PSL might be effective not only for inducing remission but also for maintenance. We then divided the patients with VDZ continuation into the VDZ+rPSL and non-VDZ+rPSL groups and evaluated them using Kaplan–Meier analysis, which showed a significant difference in the failure-free rate. After introducing VDZ, we tapered off PSL if clinical remission or a clinical response was achieved. VDZ is a humanized monoclonal antibody that selectively antagonizes the $\alpha 4\beta 7$ gastrointestinal integrin receptor and inhibits lymphocyte migration into tissues to achieve its anti-inflammatory effects [7]. VDZ is distinct from other biological therapies that target inflammatory cytokines in that it does not directly suppress these cytokines; some patients take longer to respond to VDZ or fail to respond. In contrast, VDZ demonstrates low immunogenicity and a reduced loss of response, making it a promising candidate for sustained therapeutic management. Yamashita et al. [16] reported that among 37 patients with UC who tested positive for anti-VDZ antibodies at week 30 post-VDZ administration, only one patient (2.7%) tested positive for blood test. We believe that combining PSL and VDZ may positively influence the continuation rate because PSL effectively induces remission in many patients when administered for a short duration; however, the adverse effects associated with prolonged PSL use remain problematic.

The GEMINI study used fecal calprotectin to assess therapeutic activity, but herein, we did not measure biomarkers. Therefore, we evaluated only Alb, Hb, and CRP levels and assessed their changes. CRP is a nonspecific indicator of systemic inflammation, yet it remains the most widely used biomarker for IBD in clinical practice. An improvement in CRP levels within 2–4 weeks after starting treatment with infliximab (IFX) and ADA is associated with a better prognosis in patients with UC [17–19]. In particular, Iwasa et al. [17] reported that changes in CRP levels 2 weeks after IFX induction in patients with UC could predict clinical prognosis. In our study, there was no significant improvement in the CRP levels at week 2 in any patient. However, when the VDZ+rPSL and non-VDZ+rPSL groups were further divided, the VDZ+rPSL group showed significantly improved CRP levels by week 2. We separately compared failure and non-failure in the VDZ+rPSL and non-VDZ+rPSL groups. In the VDZ+rPSL group, the CRP level improved significantly only in the non-failure group at week 2. Thus, our study indicated that CRP levels 2

weeks after VDZ induction may influence the continuation rate in the VDZ+rPSL group.

This study has some limitations. First, although detailed hematological findings were easy to extract, the number of enrolled patients was small; therefore, the sample size was not large enough to draw reliable conclusions. Second, in contrast to larger clinical trials, our retrospective study lacked a well-defined dosage regimen for PSL; therefore, the inclusion criteria might have introduced a bias. Third, no studies have been conducted on the evaluation of biomarkers such as fecal calprotectin and mucosal or histological evaluations before and after VDZ treatment. Nevertheless, despite the limited sample size in this study, Kaplan–Meier analysis revealed significant differences, reinforcing the notion that combining PSL and VDZ enhances prognosis in patients with UC.

Conclusions

Initiating treatment by combining VDZ and PSL in patients with moderate-to-severe UC may improve the long-term prognosis. Our results also indicated that CRP levels 2 weeks after VDZ induction can influence the continuation rate in the VDZ+rPSL group.

Abbreviations

ADA	Adalimumab
Alb	Albumin
CAI	Clinical activity index
CD	Crohn's disease
CRP	C-reactive protein
Hb	Hemoglobin
IBD	Inflammatory bowel disease
IFX	Infliximab
MES	Mayo Endoscopic Subscore
PSL/rPSL	Prednisolone/rapid prednisolone
UC	Ulcerative colitis
VDZ	Vedolizumab

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None.

Author contributions

YY contributed to this work. YY, NI, and KS designed the study. YY, NI, RT, AM, YY2, YH, HH, and KS collected the data. TT, KT, YA, ST, TM, MY, and YH analyzed the data. YY and NI wrote the paper. MI, TY, SO, YO, HH, and KS provided critical insight regarding paper preparation. All authors read and approved the final manuscript.

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Data availability

All data required to evaluate the conclusions of this study are presented herein. Additional data related to this study can be requested from the authors.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of the Seirei Hamamatsu General Hospital (approval number 3932). This study was conducted in accordance with the principles of Good Clinical Practice and in adherence to the Declaration of Helsinki. Informed consent was

obtained through an opt-out method, and the study details were posted on the hospital website.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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