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Examination on Factors Affecting Symptom Change after Drug Withdrawal in Patients with Mild Erosive Gastroesophageal Reflux Disease Undergoing Symptom-Controlled Maintenance Therapy with Acid-Secretion Inhibition Drugs

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Keywords
Gastroesophageal reflux disease · Rebound · Proton pump inhibitor · Vonoprazan

Abstract
Introduction: In patients with gastroesophageal reflux disease (GERD) on maintenance therapy with acid-suppressive drugs, it is not clear what background factors allow patients to discontinue the drugs. The aims of this study were to examine the relationship of the changes in the frequency and severity of gastrointestinal symptoms after discontinuation of acid-secretion inhibitors for erosive GERD (eGERD) with possible patient background factors and to identify factors that influence these changes. ***Methods:*** This is a multicenter, open-label, interventional, exploratory study. eGERD patients with mild mucosal injury whose symptoms were under control and who were on maintenance therapy with acid-suppressive drugs were withdrawn from the drug treatment for 4 weeks. We examined the relationship of patient backgrounds (sex, age, body mass index, alcohol consumption, smoking habits), esophageal hiatal hernia, *Helicobacter pylori* infection, pepsinogen I and II concentrations and I/II ratios, blood gastrin levels before and after drug discontinuation with total score change in Frequency Scale for the Symptoms of GERD (FSSG). ***Results:*** Of the 92 patients whose symptoms could be assessed before and after drug withdrawal, 66 patients (71.7% of the total) had FSSG <8 and no symptom relapse after the withdrawal. Furthermore, patient background factors that may be related to symptom relapse/non-relapse were examined, but no related factors were detected. The maintenance medications before discontinuation in the above 92 patients were a proton pump inhibitor (PPI) and vonoprazan (VPZ, a potassium ion competitive acid blocker). Since PPI and VPZ were administered to about the same number of patients, though incidentally, we additionally examined the relationship between patient

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background factors and symptom relapse/non-relapse by treatment group. As a result, no relevant background factors were detected in both groups. Although there were no significant differences between the two groups, the severity and frequency of symptom recurrence in the VPZ group tended to be higher than in the PPI group. ***Conclusions:*** Consideration of background factors is unlikely to be required in the discontinuation of maintenance therapy for eGERD. There was no significant difference in the extent of disease or frequency of recurrence during the discontinuation period, regardless of whether the drug before discontinuation was a PPI or VPZ.

Introduction

Gastroesophageal reflux disease (GERD) is a disease with an extremely high recurrence rate and requires long-term management even in case of the symptoms are mild [1–7]. Proton pump inhibitors (PPIs) or vonoprazan (VPZ), a potassium-competitive acid blocker (P-CAB) with a stronger effect than PPIs, are the first choice for medication of GERD in Japan [1].

When symptoms are once improved by the initial treatment with acid-secretion inhibition drugs (ASIDs), the maintenance, intermittent, on-demand, and step-down therapies have been used to prevent recurrence by administering the lowest necessary dose of ASIDs in the subsequent long-term management and recommended in the Japanese Guidelines for the Treatment of GERD 2015 [8], 2021 [1], and the US Guidelines [9]. The reasons for keeping acid suppression to the lowest necessary dose include avoiding the risk of side effects including neuroendocrine tumors [10–13] and *Clostridioides difficile* infection [14] associated with hypergastrinemia, which are concerns about long-term acid suppression, and cost-effectiveness [15]. PPI/P-CAB administration decreases gastric acid concentrations, but in this case, an increase in blood gastrin concentration is observed in many patients to maintain homeostasis. It has been reported that at least one of the mechanisms of GERD exacerbated by antioxidant dose reduction (including tapering) or discontinuation is an increase in gastrin concentration [15]. Based on this report, we determined that keeping gastrin levels low is important for reducing recurrence of GERD symptoms and measured gastrin levels.

There are, however, questions about common factors in GERD patients who can discontinue ASIDs and about factors affecting the duration of discontinuation. Furthermore, there are no detailed reports on symptom recurrence after the discontinuation of maintenance therapy with VPZ. In this study, we exploratively investigated factors associated with the change and incidence of symptoms after drug discontinuation in erosive GERD (eGERD) patients whose symptoms were controlled by maintenance therapy with ASIDs.

Materials and Methods

Study Design

This is a multicenter, open-label, interventional, exploratory study to determine the frequency and severity of recurrence of gastrointestinal symptoms after discontinuation of ASIDs for eGERD and to explore factors that may influence the symptoms. The Gastrointestinal Endoscopy Center at Osaka Medical and Pharmaceutical University Hospital lead to this study from November 2017 to November 2020. The Ethics Committee of each institution reviewed the protocol. Upon obtaining permission, the study was conducted in accordance with the Declaration of Helsinki and the Japanese Guidance on Clinical Trials, and the subjects were fully informed about the study in advance and provided written informed consent.

Subjects

The inclusion criteria were as follows: (1) eGERD patients diagnosed as grade A/B minor mucosal injury by Los Angeles (LA) classification on upper gastrointestinal endoscopy, (2) patients treated with ASIDs at maintenance doses for ≥1 month, and (3) patients whose symptoms had improved to a total score of <8 in the subsequent questions on a patient self-completion questionnaire for the Frequency Scale for the Symptoms of GERD (FSSG). The exclusion criteria were as follows: subjects with severe mucosal injury of grade C/D in the LA classification, considering serious complications (bleeding and stenosis) associated with discontinuation of ASIDs.

Case Setting

Based on a previous report [4], the incidence of symptoms after 4 weeks without treatment was assumed to be 40%. The number of target patients was set to 150 for which the 95% confidence interval of the incidence rate could be obtained with a precision of within ±10% (significance level 5% on both sides).

Methods

The treatment with ASIDs was stopped for the included patients. Based on a previous report [16], the observation period after discontinuation was set at 4 weeks.

Blood pepsinogen I and II levels including I/II ratio and blood *Helicobacter pylori* antibodies were measured at the time of withdrawal, and blood gastrin levels were measured at the initiation of withdrawal and week 4 after withdrawal. The subjects were handed sheets of FSSG [17], Gastrointestinal Symptom Rating Scale (GSRS) [18], and Hospital Anxiety and Depression Scale (HADS) [19] at the withdrawal and asked to complete the sheets at the initiation of withdrawal and weeks 1, 2, 3, and 4. The symptom questionnaires were collected at the visit after week 4. The survey items in the question-

Table 1. Patient background and treatment on day 1 by conventional PPI and VPZ dose groups

Factor	Item	No. of subjects or mean ± SD	Min-Med-Max	*p* value
Patient background	Sex: male (%)/female (%)			
	Entire population (*n* = 93)	55 (59.1%)/38(40.9%)		
	PPI (*n* = 47)	33 (70.2%)/14 (29.8%)		0.036[a]
	VPZ (*n* = 46)	22 (47.8%)/24 (52.2%)		
	Age (year)			
	Entire population (*n* = 93)	64.8±13.7	25.0-68.0-93.0	
	PPI (*n* = 47)	67.4±11.4	40.0-70.0-93.0	0.067[b]
	VPZ (*n* = 46)	62.2±15.4	25.0-68.0-79.0	
	Height (cm)			
	Entire population (*n* = 93)	161.78±9.04	140.00-162.00-183.00	
	PPI (*n* = 47)	163.30±9.03	145.00-163.50-180.00	0.103[b]
	VPZ (*n* = 46)	160.24±8.88	140.00-160.00-183.00	
	Weight (kg)			
	Entire population (*n* = 93)	62.94±11.41	35.20-63.00-106.00	
	PPI (*n* = 47)	62.31±10.49	35.20-63.00-83.00	0.598[b]
	VPZ (*n* = 46)	63.57±12.37	46.30-62.25-106.00	
	BMI (kg/m^2)			
	Entire population (*n* = 93)	23.96±3.38	16.20-23.80-41.00	
	PPI (*n* = 47)	23.28±2.89	16.20-23.20-29.10	0.048[b]
	VPZ (*n* = 46)	24.66±3.71	19.30-24.45-41.00	
	Blood gastrin (pg/mL)			
	Entire population (*n* = 92)	587.2±510.0	10.0-455.0-2,500	
	PPI (*n* = 47)	383.3±281.7	10.0-280.0-1,300	<0.001[b]
	VPZ (*n* = 45)	800.3±603.5	69.0-620.0-2,500	
	Blood pepsinogen I (ng/mL)			
	Entire population (*n* = 92)	173.07±159.68	24.10-135.50-1,040.00	
	PPI (*n* = 47)	127.96±70.14	24.10-120.00-285.00	0.005[b]
	VPZ (*n* = 45)	220.20±207.71	25.30-153.00-1,040.00	
	Blood pepsinogen II (ng/mL)			
	Entire population (*n* = 92)	31.47±29.76	4.70-22.35-173.00	
	PPI (*n* = 47)	20.84±10.71	4.70-19.30-52.40	<0.001[b]
	VPZ (*n* = 45)	42.58±38.27	7.30-30.80-173.00	
	Pepsinogen I/II ratio			
	Entire population (*n* = 92)	5.71±1.70	1.50-5.60-10.00	
	PPI (*n* = 47)	6.17±1.84	2.70-6.10-10.00	0.008[b]
	VPZ (*n* = 45)	5.24±1.40	1.50-5.40-9.60	
	Smoking habit: yes/no			
	Entire population (*n* = 92)	20 (21.7%)/72 (78.3%)		
	PPI (*n* = 47)	10 (21.3%)/37 (78.7%)		1.000[a]
	VPZ (*n* = 45)	10 (22.2%)/35 (77.8%)		
	Alcohol drinking: yes/no			
	Entire population (*n* = 92)	56 (60.9%)/36 (39.1%)		
	PPI (*n* = 47)	30 (63.8%)/17 (36.2%)		0.670[a]
	VPZ (*n* = 45)	26 (57.8%)/19 (42.2%)		
	LA classification of GERD			
	Entire population (*n* = 93)	A: 62 (66.7%), B: 31 (33.3%)		
	PPI (*n* = 47)	A: 36 (76.6%), B: 11 (23.4%)		0.049[a]
	VPZ (*n* = 46)	A: 26 (56.5%), B: 20 (43.5%)		
	Treatment period of GERD: month (<3, ≥3 but <12, ≥12)			
	Entire population (*n* = 92)	63 (68.5%)/10 (10.9%)/19 (20.7%)		
	PPI (*n* = 46)	30 (65.2%)/4 (8.7%)/12 (26.1%)		0.426[a]
	VPZ (*n* = 46)	33 (71.7%)/6 (13.0%)/7 (15.2%)		
	Esophageal hiatus hernia: yes/no			
	Entire population (*n* = 93)	46 (49.5%)/47 (50.5%)		

Table 1 (continued)

Factor	Item	No. of subjects or mean ± SD	Min-Med-Max	*p* value
	PPI (*n* = 47)	24 (51.1%)/23 (48.9%)		
	VPZ (*n* = 46)	22 (47.8%)/24 (52.2%)		0.837[a]
	Complication[c]: yes/no			
	Entire population (*n* = 93)	62 (66.7%)/31 (33.3%)		
	PPI (*n* = 47)	31 (66.0%)/16 (34.0%)		
	VPZ (*n* = 46)	31 (67.4%)/15 (32.6%)		1.000[a]
	H. pylori antibody in blood: –/+/false positive			
	Entire population (*n* = 92)	85 (92.4%)/5 (5.4%)/2 (2.2%)		
	PPI (*n* = 47)	43 (91.5%)/3 (6.4%)/1 (2.1%)		1.000[a]
	VPZ (*n* = 45)	42 (93.3%)/2 (4.4%)/1 (2.2%)		
Treatment	Agents for digestive organs other than acid-secretion inhibitors: yes/no			
	Entire population (*n* = 93)	4 (4.3%)/89 (95.7%)		
	PPI (*n* = 47)	2 (4.3%)/45 (95.7%)		1.000[a]
	VPZ (*n* = 46)	2 (4.3%)/45 (95.7%)		
	Other concomitant drugs: yes/no			
	Entire population (*n* = 93)	51 (54.8%)/42 (45.2%)		
	PPI (*n* = 47)	24 (51.1%)/23 (58.7%)		0.534[a]
	VPZ (*n* = 46)	27 (58.7%)/19 (41.3%)		

BMI, body mass index; GERD, gastroesophageal reflux disease; LA, Los Angeles; Max, maximum, Med, median; Min, minimum; No., no. of patients; SD, standard deviation; Week 4: at 4 weeks from the starting day of drug withdrawal. * Comparison between groups with FSSG<8 and FSSG≥8. [a] Fishers' exact probability test. [b] Unpaired *t*-test. [c] Hepatitis B, epilepsy, Graves' disease, rheumatism, diarrhea, hay, fever, Hashimoto's disease, mild aortic stenosis, thyroid cancer, hypothyroidism, hyperthyroidism, hyperuricemia, hemorrhoids, postoperative prostate cancer, prostatic hyperplasia, BPH, inguinal hernia, appendicitis surgery, ulcerative colitis (remission period), mucous membrane healing, skin disease, insomnia, constipation.

naires and case reports are those described in Table 1 in addition to types/dosage of ASIDs, gastrointestinal drugs other than ASIDs, concomitant drugs, antiplatelet drugs excluding low-dose aspirin, anticoagulants, steroids, and bisphosphonates. The intake of drugs including gastroprokinetic agents and antagonists of PPI, P-CAB, and H_2-receptor affecting the study results was prohibited.

Evaluation and Statistical Analysis

We examined the association of the variation in FSSG total score with items given in Table 1. Secondary endpoints were to examine the variations in the scores of GSRS, FSSG (reflux, dyskinesia), and HADS (depression) including subscales and factors affecting the variations.

Regarding the statistical methods employed, frequencies and percentages of background factors were presented as nominal and ordinal scales, and summary statistics were calculated for continuous quantities. The unpaired *t*-test and Fisher's exact probability test were performed according to the nature of the data. Each endpoint on day 1 and at each measurement time point was analyzed using a paired *t*-test, while single regression analysis was used for the change in FSSG and GSRS scores. Hypothesis tests were two-tailed, and the significance level was set at 5% without considering multiplicity because the purpose was exploratory evaluation. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

When setting up the study, the target number of enrolled patients was set at 150, but in reality, the planned number of patients was unable to be collected within the study period; thus, totaling 99 patients were enrolled. Of these, 93 subjects for whom FSSG scores on day 1 were available were included in the analyses.

Patient Background

Table 1 summarizes the summary statistics (mean ± SD) on day 1 for the background factors and treatment factors that may affect eGERD treatment and shows the values for the entire patient population and for the respective PPI and VPZ groups, though the primary endpoint targeted the entire population only. Of the included 93 patients, male and female were 55 (59.1%) and 38 (40.9%), respectively, without significant difference. Seventy subjects (75.3% of the total) were over 60 years of age. The drugs administered were either PPIs (esomeprazole: 27 cases, omeprazole: 1 case, rabeprazole: 15 cases, lansoprazole: 4 cases), or VPZ (46 cases).

Table 2. Patient background and treatment at week 4 by group with FSSG<8 and group with FSSG≥8

Factor	Item	No. of subjects or mean ± SD	Min-Med-Max	*p* value
Patient background	Sex: male (%)/female (%)			
	Entire population (*n* = 92)	54 (58.7%)/38 (58.7%)		
	FSSG<8 (*n* = 66)	40 (60.6%)/26 (39.4%)		0.640[a]
	FSSG≥8 (*n* = 26)	14 (53.8%)/12 (46.2%)		
	Age (year)			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	64.1±13.8	25.0-68.0-93.0	0.499[b]
	FSSG≥8 (*n* = 26)	66.3±13.6	31.0-70.5-83.0	
	Height (cm)			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	162.30±9.72	140.00-163.05-183.00	0.433[b]
	FFSSG≥8 (*n* = 26)	160.65±7.19	147.00-160.65-174.00	
	Weight (kg)			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	63.36±11.97	46.30-62.00-106.00	0.613[b]
	FSSG≥8 (*n* = 25)	62.01±10.24	16.20-64.20-29.30	
	BMI (kg/m^2)			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	23.97±3.49	18.60-23.70-41.00	0.958[b]
	FSSG≥8 (*n* = 26)	23.93±3.22	19.30-24.35-41.00	
	Blood gastrin (pg/mL)			
	Entire population (*n* = 91)			
	FSSG<8 (*n* = 66)	575.0±534.6	10.0-430.0-2,500.0	0.770[b]
	FSSG≥8 (*n* = 25)	610.5±457.4	83.0-490.0-1,600.0	
	Blood pepsinogen I (ng/mL)			
	Entire population (*n* = 91)			
	FSSG<8 (*n* = 66)	174.74±176.09	24.10-135.50-1,040.00	0.897[b]
	FSSG≥8 (*n* = 25)	169.83±112.43	41.70-129.00-555.00	
	Blood pepsinogen II (ng/mL)			
	Entire population (*n* = 91)			
	FSSG<8 (*n* = 66)	32.21±33.45	4.70-21.55-173.00	0.618[b]
	FSSG≥8 (*n* = 25)	28.68±17.33	9.40-22.40-76.50	
	Pepsinogen I/II ratio			
	Entire population (*n* = 91)			
	FSSG<8 (*n* = 66)	5.66±1.75	1.50-5.65-10.00	0.443[b]
	FSSG≥8 (*n* = 25)	5.97±1.49	3.00-5.60-9.60	
	Smoking habit: yes/no			
	Entire population (*n* = 91)			
	FSSG<8 (*n* = 65)	15 (23.1%)/50 (76.9%)		0.785[a]
	FSSG≥8 (*n* = 26)	5 (19.2%)/21 (80.8%)		
	Alcohol drinking (no.): yes/no			
	Entire population (*n* = 91)			
	FSSG<8 (*n* = 65)	38 (58.5%)/27 (41.5%)		0.638[a]
	FSSG≥8 (*n* = 26)	17 (65.4%)/9 (34.6%)		
	LA classification of GERD			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	A: 48 (72.7%), B: 18 (27.3%)		0.091[a]
	FSSG≥8 (*n* = 26)	A: 14 (53.8%), B: 12 (46.2%)		
	Treatment period of GERD (month)			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	<3: 47 (72.3%), ≥3 but <12: 7 (10.8%), ≥12: 11 (16.9%)		0.510[a]
	FSSG≥8 (*n* = 26)	<3: 16 (61.5%), ≥3 but <12: 3 (11.5%), ≥12: 7 (26.9%)		
	Oesophageal hiatus hernia: yes/no			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	31 (47.0%)/55 (53.0%)		0.645[a]
	FSSG≥8 (*n* = 26)	14 (53.8%)/12 (46.2%)		

Table 2 (continued)

Factor	Item	No. of subjects or mean ± SD	Min-Med-Max	*p* value
	Complication [c]: yes/no			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	45 (68.2%)/21 (31.8%)		0.626[a]
	FSSG≥8 (*n* = 26)	16 (61.5%)/10 (38.5%)		
	H. pylori antibody in blood: −/+/indeterminable			
	Entire population (*n* = 91)			
	FSSG<8 (*n* = 65)	61 (93.8%)/4 (6.2%)/0 (0.0%)		0.388[a]
	FSSG≥8 (*n* = 26)	24 (92.3%)/1 (3.8%)/1 (3.8%)		
Treatment	Type of acid-secretion inhibitors: H2-receptor antagonist/PPI/VPZ			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	0 (0%)/33 (50.0%)/33 (50.0%)		1.000[a]
	FSSG≥8 (*n* = 26)	0 (0%)/13 (50.0%)/13 (50.0%)		
	Agents for digestive organs other than acid-secretion inhibitors: yes/no			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	1 (1.5%)/65 (98.6%)		0.067[a]
	FSSG≥8 (*n* = 26)	3 (11.5%)/23 (88.6%)		
	Other concomitant drugs: yes/no			
	Entire population (*n* = 92)			
	FSSG<8 (*n* = 66)	36 (54.5%)/30 (45.5%)		1.000[a]
	FSSG≥8 (*n* = 26)	14 (53.8%)/12 (46.2%)		

BMI, body mass index; FSSG, Frequency Scale for the symptom of GERD; GERD, gastroesophageal reflux disease; LA, Los Angeles; Max: maximum; Med, median; Min, minimum; No., number of patients; PPI, proton pump inhibitor; SD, standard deviation; VPZ, vonoprazan; Week 4, at 4 weeks from the starting day of drug withdrawal. * Comparison between FSSG<8 and FSSG≥8. [a] Fishers' exact probability test. [b] Unpaired *t*-test. [c] Hepatitis B, epilepsy, Graves' disease, rheumatism, diarrhea, hay, fever, Hashimoto's disease, mild aortic stenosis, thyroid cancer, hypothyroidism, hyperthyroidism, hyperuricemia, hemorrhoids, postoperative prostate cancer, prostatic hyperplasia, BPH, inguinal hernia, appendicitis surgery, ulcerative colitis (remission period), mucous membrane healing, skin disease, insomnia, constipation.

Table 3. Change of gastrin concentration in blood (pg/mL)

		Day 1	Week 4	Variation	*p* value*
Entire population[a]	Mean±SD	587.2±510.05	153.97±197.58	−430.55±516.26	<0.0001
	Min-Med-Max	10-455-2,500	10-97.5-1,500	−2,416- −300-500	
PPI dose group[b]	Mean±SD	383.26±281.74	144.54±172.70	−229.43±279.74	<0.0001
	Min-Med-Max	10-280-1,300	10-95.5-970	−1,190- −1,76.5-290	
VPZ dose group[c]	Mean±SD	800.27±603.48	163.39±221.22	−636.13±616.13	<0.0001
	Min-Med-Max	69-620-2,500	46-99-1,500	−2,416- −470-500	

Variation: values obtained by subtracting the values on day 1 from those at week 4. Day 1, the time of drug withdrawal; Max, maximum; Med, median; Min, minimum; VPZ, vonoprazan; PPI, proton pump inhibitor; SD, standard deviation; Week 4, 4 weeks after drug discontinuation. * Comparison between day 1 and week 4 by using the paired *t*-test. [a] *n* = 92 but *n* = 91 for variation because of 1 missing value on day and at week 4. [b] *n* = 47 on day 1, but *n* = 46 at week 4 and for variation. [c] *n* = 45 on day 1 and for variation, and *n* = 46 at week 4.

Although it was not initially set as an endpoint, since almost the same number of patients (*N* = 45–47) were included in each PPI and VPZ group, we deviated from protocol to conduct intergroup comparison, and Table 1 gives the data for the respective groups. The results show that there were statistically significant intergroup differences ($p < 0.05$) for sex, BMI, blood gastrin levels, blood pepsinogen I, II levels, I/II ratios, and LA classification A/B but no intergroup differences in other parameters.

Table 4. Covariance analysis of variation of blood gastrin between PPI and VPZ dose groups

	Mean least squares	Standard error	Pr > |t|
PPI dose group	−425.0482	30.6515	$p < 0.001$
VPZ dose group	−436.1729	31.0229	$p < 0.001$
	Mean least squares	95% confidence limit	Pr > |t|
Difference (PPI – VPZ)	11.1247	−79.6026 to 101.8519	$p = 0.808$

Covariate: variation from day 1. Day 1, registration time; PPI, proton pump inhibitor; VPZ, vonoprazan; Week 4, week 4 from the initiation of drug withdrawal.

Table 5. Change of FSSG total score

Observation period	No. of patients	Mean ± SD	Min-Med-Max	*p* value*
PPI + VPZ dose groups				
Day 1	93	2.2±2.3	0-2-7	
Week 1	93	4.8±2.6	0-3-26	<0.001
Week 2	92	5.9±6.4	0-4-28	<0.001
Week 3	92	6.2±6.9	0-4-35	<0.001
Week 4	92	6.3±7.0	0-5-37	<0.001
PPI dose group				
Day 1	47	2.0±2.3	0-1-7	
Week 1	47	3.8±4.8	0-2-23	0.001
Week 2	46	4.9±6.3	0-3-28	<0.001
Week 3	46	5.2±6.9	0-3.5-35	0.001
Week 4	46	5.3±6.7	0-3-32	<0.001
VPZ dose group				
Day 1	46	2.4±2.3	0-2-7	
Week 1	46	5.7±6.1	0-2-26	<0.001
Week 2	46	6.9±6.3	0-5-23	<0.001
Week 3	46	7.2±6.7	0-5-33	<0.001
Week 4	46	7.2±7.3	0-5-37	<0.001

FSSG, Frequency Scale for the Symptom of GERD; Max, maximum; Med, median; Min, minimum; PPI, proton pump inhibitor; SD, standard deviation; VPZ, vonoprazan. * Comparison of the values at each week with those on day 1 determined by paired *t*-test.

Symptom Relapse after Drug Withdrawal, Non-Relapse Factors, and Change in Blood Gastrin Level

Mean ± SD of summary statistics at week 4 for the same items as in Table 1 is shown for entire population and the patients stratified by FSSG <8 (non-relapse) and FSSG≥ 8 (relapse) (Table 2). Although symptoms of 92 patients could be assessed just before and after the withdrawal, since there were some subjects missing some data for the items on day 1 or week 4, the evaluation of variations could be performed in 91 cases. Of the 91 patients, 66 (72.5%) had FSSG <8 after the withdrawal.

There was no statistically significant difference ($p < 0.05$) between the patients with FSSG< 8 and FSSG≥ 8 in any of the items examined, and there was no association of symptom relapse with any of the factors. Table 3 shows the respective blood gastrin levels and variations from day 1 to week 4 for entire population and the patients in each group. The amount of variation was significantly lower at week 4. Since there was already a significant intergroup difference on day 1, we performed a covariance analysis using the day 1 values as covariates; the intergroup difference was statistically insignificant at $p = 0.808$ (Table 4).

Symptom Transition after Drug Suspension

Table 5 shows the FSSG total scores at day 1 and each week for entire population and the patients in the two groups. The total scores at each week were higher than those on day 1 with statistical significance ($p < 0.001$) in the two dose groups and entire population. Comparison

Table 6. Change of FSSG sub-score related to acid reflux

Observation period	No. of patients	Mean ± SD	Min-Med-Max	*p* value*
PPI + VPZ dose groups				
Day 1	92	1.0±1.3	0-0-5	<0.001
Week 1	92	2.9±3.8	0-1.5-20	<0.001
Week 2	92	3.4±3.8	0-2-14	<0.001
Week 3	92	3.8±4.3	0-3-20	<0.001
Week 4	92	3.7±4.4	0-3-24	
PPI dose group				
Day 1	46	1.0±1.3	0-0-5	
Week 1	46	2.2±3.1	0-1-14	<0.001
Week 2	46	2.8±3.7	0-1-14	<0.001
Week 3	46	3.2±4.2	0-1.5-19	<0.001
Week 4	46	3.0±3.8	0-1-15	<0.001
VPZ dose group				
Day 1	46	1.0±1.3	0-0-4	
Week 1	46	3.5±4.3	0-3-20	<0.001
Week 2	46	4.1±3.9	0-2-14	<0.001
Week 3	46	4.5±4.3	0-3-20	<0.001
Week 4	46	4.5±4.8	0-3-24	<0.001

FSSG, Frequency Scale for the Symptom of GERD; Max, maximum; Med, median; Min, minimum; PPI, proton pump inhibitor; SD, standard deviation; VPZ, vonoprazan. * Comparison of the values at each week with those on day 1 determined by paired *t*-test.

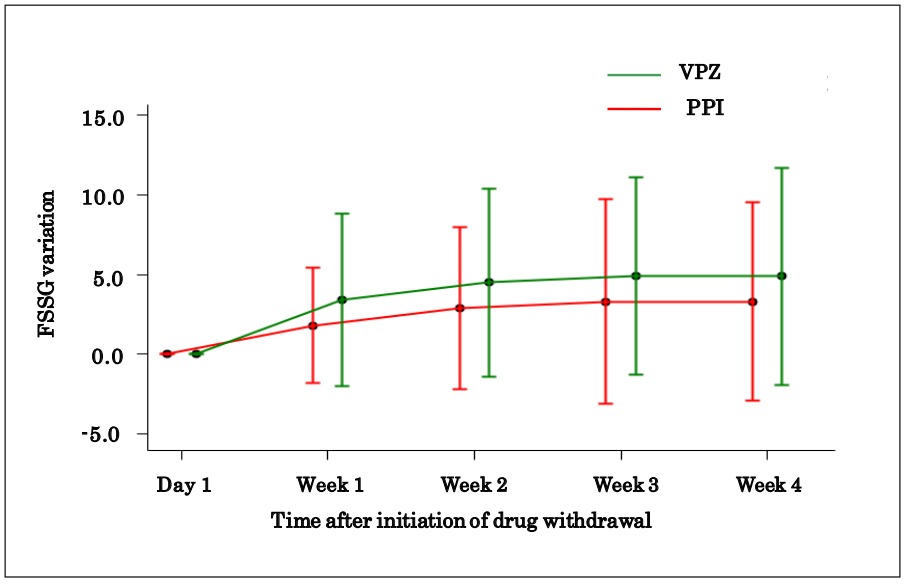

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Fig. 1. Change of variation of FSSG total score from day 1. No. of patients: 46–47 in PPI dose group and 46 in VPZ dose group. PPI, proton pump inhibitor; VPZ, vonoprazan; day 1, initial day of drug withdrawal; week 1 to week 4, measurement weeks after drug withdrawal.

of the two groups for the variations in FSSG total scores at each time point (unpaired *t*-test) demonstrates that the VPZ group was higher than the PPI group, though without statistical significance (shown in Fig. 1). The results of the sub-scores by acid reflux-related symptom and motor deficiency symptom are shown in Tables 6, 7, respectively. The comparison of the amount of variation in the FSSG sub-scores at each time point shows an increasing trend over time without significant difference, and the comparison of the two groups (unpaired *t*-test) shows no significant difference. However, all the sub-scores were higher in the VPZ group than those in the PPI group at each time point (shown in Fig. 2, 3).

Next, we examined the GSRS total scores/sub-scores and the HADS scores; between day 1 and each time point, there was no significant difference in the amount of variations in

Table 7. Change of FSSG sub-score related to dysmotility

Observation period	No. of patients	Mean ± SD	Min-Med-Max	*p* value*
PPI + VPZ dose groups				
Day 1	93	1.2±1.5	0-1-7	
Week 1	93	1.9±2.2	0-1-9	<0.001
Week 2	92	2.5±2.9	0-1-15	<0.001
Week 3	92	2.4±3.0	0-1-16	<0.001
Week 4	92	2.5±3.1	0-2-17	<0.001
PPI dose group				
Day 1	47	1.1±1.4	0-0-5	
Week 1	47	1.6±2.2	0-1-9	0.022
Week 2	46	2.1±3.0	0-1-15	0.004
Week 3	46	2.0±3.2	0-1-16	0.021
Week 4	46	2.3±3.4	0-1-17	0.009
VPC dose group				
Day 1	47	1.3±1.7	0-1-7	
Week 1	47	2.2±2.3	0-2-9	0.002
Week 2	46	2.8±2.8	0-2-10	<0.001
Week 3	46	2.8±2.8	0-2-13	<0.001
Week 4	46	2.8±2.8	0-2-13	<0.001

FSSG, Frequency Scale for the Symptom of GERD; Max, maximum; Med, median; Min, minimum; PPI, proton pump inhibitor; SD, standard deviation; VPZ, vonoprazan. * Comparison of the values at each week with those on day 1 determined by paired *t*-test.

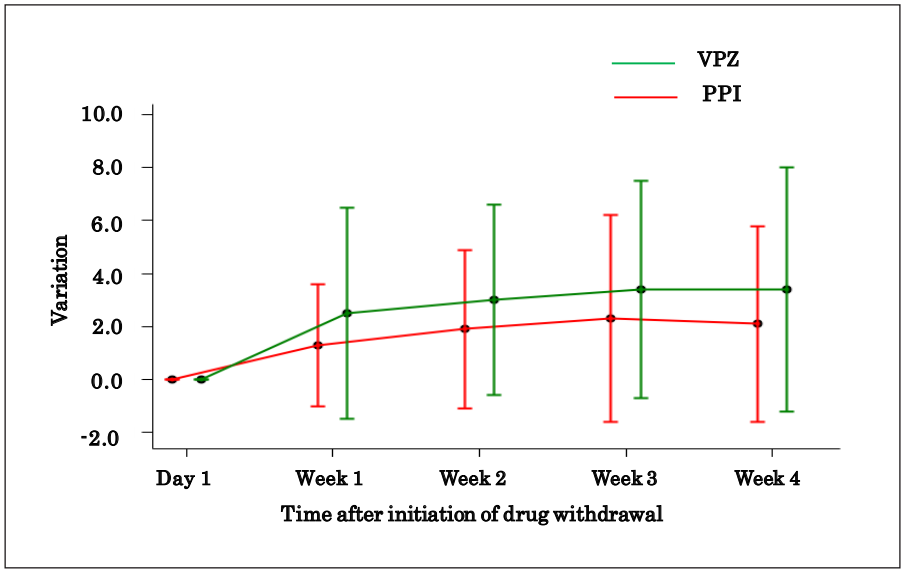

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Fig. 2. Change of variation of FSSG sub-score related to acid reflux from day 1. No. of patients: 46 in each dose group. PPI, proton pump inhibitor; VPZ, vonoprazan; day 1, initial day of drug withdrawal; week 1 to week 4, measurement weeks after drug withdrawal.

the HADS scores, but the difference in the GSRS total score was significant at $p < 0.001$. There were also significant differences in the subscales of acid reflux and abdominal pain. Indigestion, diarrhea, and constipation, however, show no significant difference (See Table 1 in Supplementary file).

The percentage of subjects with FSSG total score of ≥8 in the two groups and entire population was calculated using the number of subjects on day 1 as the denominator (shown in Fig. 4). To assess whether the distribution of FSSG total score (<8/≥8) at each time point differed among the ASIDs, we compared it by Fisher's exact probability test. As a result, no statistically significant difference was obtained at any time points. The number of subjects in the VPZ group with FSSG total score of ≥8, however, remained around 30% except for 39.1% at week 3. In the PPI group, the number of subjects with FSSG total score of ≥8 showed

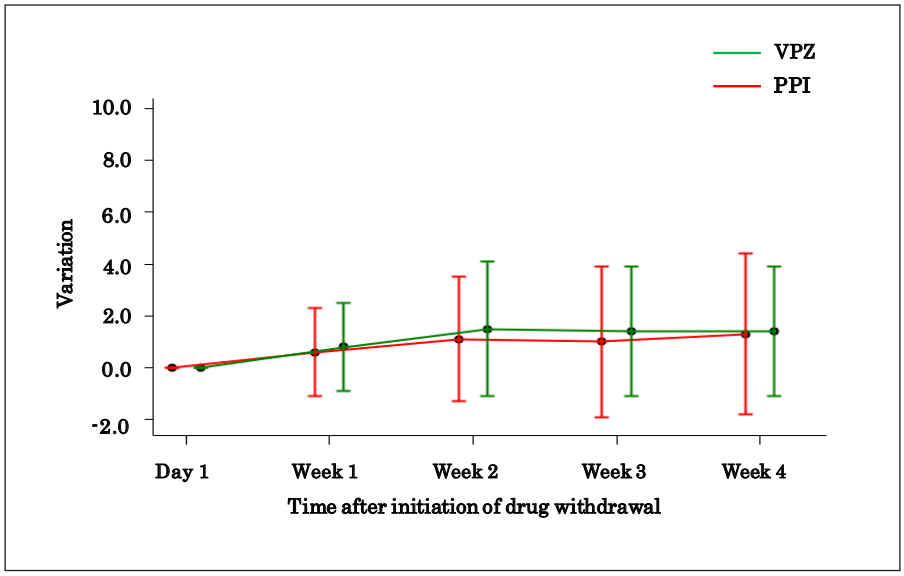

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Fig. 3. Change of variation of FSSG subscore related to dysmotility from day 1. No. of patients: 46–47 in each dose group. PPI, proton pump inhibitor; VPZ, vonoprazan; day 1, initial day of drug withdrawal; week 1 to week 4, measurement weeks after drug withdrawal.

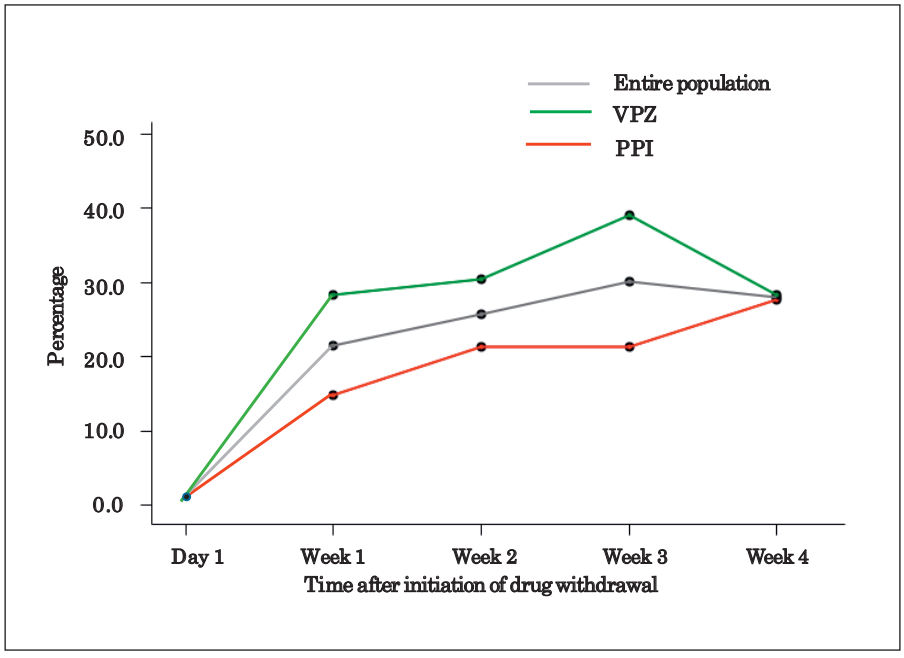

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Fig. 4. Percentage of patients showing FSSG total score of 8 or higher at each time point. No. of patients: 46–47 in each dose group. PPI, proton pump inhibitor; VPZ, vonoprazan; day 1, initial day of drug withdrawal; week 1 to week 4, measurement weeks after drug withdrawal. Statistical analysis: paired *t*-test.

an upward tendency over time from approximately 15–21% except for 27.7% at week 4.

A single regression analysis was performed with the amount of variations in FSSG total scores at week 4 as the objective variable and the background factors of continuous volume (age, BMI, blood gastrin levels, and pepsinogen I/II ratios at enrollment) and questionnaire results at the enrollment (total scores of FSSG, GSRS, and HADS) as explanatory variables. No statistically significant correlations were observed for any of the factors and for the FSSG subscores. Single regression analysis of the variations in GSRS subscores at week 4 shows weak correlations with BMI of 0.2562 for the acid reflux subscore, day 1 blood gastrin level of 0.2081 for abdominal pain, and age of 0.2874 for the constipation score (See Table 2 of Supplementary file).

Discussion

The above results demonstrate that we could suspend the ASIDs for at least 4 weeks in nearly 70% of eGERD patients with mild mucosal injury under control on main-

tenance therapy with ASIDs. The primary endpoint of this study was to examine patient background factors affecting drug withdrawal in the entire patient population, but we could not identify such factors in practice. Manabe et al., [20], on the other hand, identified the following risk factors for exacerbation of mucosal laceration in patients with mild reflux esophagitis: increasing age, female, endoscopic symptoms at initial presentation, hiatal hernia, atrophic gastritis, and *H. pylori* infection. The reason for the difference in results between the two studies may be that Manabe et al. targeted the untreated group, whereas ours targeted the treated group.

Each patient received either PPIs or VPZ, and approximately equal numbers of patients ($n = 45–47$) were incidentally distributed in the PPI and VPZ groups (Tables 1, 2). Therefore, we tried to compare the two groups, although this was not an endpoint set in the protocol, and it is possible that symptom recurrence after withdrawal is more likely to occur in patients with severe symptoms before treatment compared to patients with mild symptoms before treatment. This point is, however, unknown because this study included patients without gastrointestinal symptoms on maintenance therapy. Among the patient backgrounds, statistically significant intergroup differences ($p < 0.05$) were observed for sex, BMI, blood gastrin levels, blood pepsinogen I and II concentrations and I/II ratios, and LA classification A/B. The higher blood gastrin levels in the VPZ group may be attributable to the higher inhibitory effect of VPZ on acid secretion than PPIs. Similar results are reported in several papers [21–23]. The reason why blood pepsinogen I/II concentrations were higher in the VPZ-treated group may be attributable to the high acid-secretion inhibition effect of VPZ. It is interesting to note that blood gastrin levels (Table 1), FSSG total scores (Table 5), and FSSG sub-scores (Tables 6, 7) were tended to be higher in the VPZ group than those in the PPI group on day 1 and week 4.

The following factors, which are likely to affect symptoms after the drug withdrawal, were examined: patient background items listed in Table 1; total score and subscores of FSSG, HADS, and GSRS; and other gastrointestinal drugs and concomitant medications in use. No correlative factors were found except for BMI exhibiting a weak correlation with the acid reflux-related GSRS subscore, and age exhibiting a weak correlation with the constipation score. The FSSG was additionally stratified into ≥8 and <8 to examine factors correlated with disease status, but no correlative factors were found (Table 2). Hence, factors that may be related to symptom recurrence were not found in this study.

There was no statistically significant intergroup difference in symptom recurrence after drug withdrawal, but there was a tendency toward a higher frequency of recurrence in the VPZ group at each week. In the VPZ group, the FSSG total score of ≥8 was around 30% at each time point, whereas in the PPI group, it was from 15% to 21% (shown in Fig. 4). This tendency toward a high relapse incidence in the VPZ group is consistent with the greater change in blood gastrin levels in this group.

The review by the American Gastroenterological Association [24] describes that PPIs have little causality with adverse events including renal impairment and dementia. We previously reported that the effect of VPZ is considerably stronger than rabeprazole belonging to PPIs; VPZ maintained a high pH even at doses as low as 1/2-1/4 times the standard dose of rabeprazole. Therefore, VPZ caused significantly higher blood gastrin levels [25]. There are no reports on serious side effects of VPZ for up to 2 years [26], but elucidation of the safety of VPZ in long-term maintenance therapy is important. This study shows that there was no significant intergroup difference ($p < 0.05$) in most of the patient background factors on day 1, except for blood gastrin level, pepsinogen levels and I/II ratios, and LA classification. Among these factors, blood gastrin levels were significantly higher in the VPZ group (383.3 ± 281.7 pg/mL) than those in the PPI group (800.3 ± 603.5 pg/mL: the finding being consistent with the description in the above report [23].

There is a report [27] affirming the acid hypersecretion by ASID discontinuation, but several articles [28–30] reported that this is not a major problem. We have, however, thought that the possibility of acid hypersecretion is important in discontinuation of drugs with strong efficacy.

If the goal is to wean patients from ASID in the treatment of GERD, it is important to keep in mind the side effects that may occur during the maintenance therapy and the need to avoid rebound after discontinuation. From these points of view, the maintenance therapy for GERD should avoid unnecessarily prolonged strong acid-secretion suppression, even if symptoms are improving.

There are several limitations to this study: (1) the number of subjects was smaller than originally planned, (2) the drug withdrawal period was 4 weeks, (3) endoscopy was not performed after the drug withdrawal, and (4) the difference between the PPI and VPZ groups observed in this study may be attributable to a bias based on the physician's prescriptions/instructions for the use of PPI and VPZ and the subject's backgrounds; thus, caution should be exercised in interpreting the present data. The respective reasons for limitations (1–3) are as follows: As for (1),

since we could not enroll the planned number of patients during the initial enrollment period, the enrollment period was extended. However, the target number of patients was not again reached, and the inclusion of the target 150 patients was abandoned midway through the study because further extension of the study period would have significantly prolonged the duration of the study. As for (2), occurrence of epigastric symptoms was examined after withdrawal of PPI and placebo in healthy subjects in a double-blind comparative study by Niklasson et al. [16]. The results show that symptoms were significantly higher in the PPI group compared to placebo for the first 2 weeks, while without difference after the third week. Based on these results, we assumed that symptoms after the withdrawal of ASIDs would be more frequent by 4 weeks after withdrawal; this was the reason why we set up to 4 weeks as the observation period. As for (3), it is desirable to conduct endoscopic examination after drug withdrawal. However, we dared to omit the endoscopic examination after drug withdrawal for the aim of (1) creating an environment that facilitates the active participation of many patients in the study as subjects and (2) collecting/providing data that can be used by physicians in many clinics who do not perform endoscopy in their daily practice. This was decided with the consent of the participating physicians when the study protocol was reviewed.

Conclusions

There were no patient factors that are likely to affect the discontinuation of maintenance therapy for eGERD. There was no significant difference in the extent of disease or frequency of recurrence during the discontinuation period, regardless of whether the drug before discontinuation was PPIs or VPZ. Since 70% of patients did not experience recurrence for at least 4 weeks and there were no serious complications even in patients experiencing recurrence, temporary discontinuation of maintenance therapy with ASIDs, especially with PPIs, is acceptable for mild eGERD.

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Statement of Ethics

The study protocol was reviewed and approved by the Ethics Committee of Osaka Medical and Pharmaceutical University Hospital followed by the Institutional Review Board of each institution before the recruitment of patients [approval number: 2018-078-3]. Upon obtaining permission, the study was conducted in accordance with the Declaration of Helsinki and the Japanese Guidance on Clinical Trials, and the subjects were fully informed about the study in advance and provided written informed consent.

Conflict of Interest Statement

The consents for participation and publication were obtained from each author who participated in this study. There were no competing interests.

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Author Contributions

Toshihisa Takeuchi: writing/reviewing/editing of original draft paper, data curation, formal analysis, methodology reviewing, and visualization. Hironori Tanaka, Shinya Nishida, Hitosi Hongo, Michiaki Takii, Takeshi Higashino, Makoto Sanomura, Hirota Miyazaki, Masahiro Hoshimoto, Tsuguhiro Kimura, Masahiro Sakaguchi, Takashi Abe, Akitoshi Hakoda, Noriaki Sugawara, Taro Iwatsubo, Shinpei Kawaguchi, Kazuhiro Ota, and Yuichi Kojima: investigation, enrollment of patients, and data collection. Kazuhide Higuchi: writing/reviewing/editing draft paper and supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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