Examination on factors affecting symptom change after drug withdrawal in patients with erosive gastroesophageal reflux disease undergoing symptom-controlled maintenance therapy with acid-secretion inhibition drugs

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Abstract

Background: 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 aim is 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mucosal injury whose symptoms were under control and who were on maintenance therapy with acid-suppressive drugs were withdrawn from the drug treatment for 4 weeks.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 background (sex, age, body mass index, alcohol consumption, smoking habits), esophageal hiatal hernia, *H. 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 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 both drugs were administered to about the same number of patients though incidentally, we examined the relationship between patient 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.

Trial registration: The study was registered in the UMIN Clinical Trial Registry (UMIN000029957).

Background

Gastroesophageal reflux disease (GERD) is a disease with an extremely high recurrence rate and requires long-term management even the symptoms are mild [1, 2-7]. 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]. The following clinical issues have been identified for PPIs: (1) the onset of effects takes several days after administration [8, 9], (2) cytochrome P450s including CYP2C19 are involved in the metabolism resulting in individual differences due to genetic polymorphisms [10-12],

(3) obtaining an inhibitory effect on acid secretion at night is difficult [13], and (4) PPIs are unstable under acidic conditions [14]. On the other hand, VPZ has been reported to almost overcome these issues [13-17], and was introduced in Japan in February 2015 [2].

When symptoms are once improved by the initial treatment with acid-secretion inhibition drugs (ASIDs), the maintenance, intermittent, on-demand, and step-down therapies are used to prevent recurrence by administering the lowest necessary dose of ASIDs in the subsequent long-term management and are recommended in the Japanese Guidelines for the Treatment of GERD 2015 [18], 2021 [1], and the US Guidelines [19]. The reasons for keeping acid suppression to the lowest necessary dose include avoiding the risk of side effects including neuroendocrine tumors [20-23] and *Clostridioides difficile* infection [24] associated with hypergastrinemia, which are concerns about long-term acid suppression, and cost-effectiveness [25]. Rapid increase in gastric acid secretion is involved in the relapse of GERD symptoms after discontinuation of ASIDs, and it is reported that the larger the change in blood gastrin level before and after discontinuation, the more likely rebound occurs [26]. Thus, when considering the discontinuation of ASIDs in the maintenance treatment of GERD, it is important to maintain blood gastrin levels as low as possible before discontinuation and keep acid-suppressive therapy to the minimum necessary.

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.

Subjects 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: (1) GERD 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 retrospective questions on a patient self-completion questionnaire for the Frequency Scale for the Symptoms of GERD (FSSG).

The exclusion criteria were: 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 [27], the observation period after discontinuation was set at 4 weeks.

Blood pepsinogen I and II levels including I/II ratio and blood *H. 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, Gastrointestinal Symptom Rating Scale (GSRS), and Hospital Anxiety and Depression Scale (HADS) 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 questionnaires 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 were prohibited.

Evaluation and statistical analysis: We examined the association of the variation in FSSG total score with items given in Table 1 (primary endpoint).

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. 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 respectively 55 (59.1%) and 38 (40.9%), 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.

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 inter-group comparison, and in Table 1 gives the data for the respective groups. The results show that there were statistically significant inter-group 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 inter-group differences in other parameters.

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 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 each group. The amount of variation was significantly lower at Week 4. Since there was already a significant inter-group difference on Day 1, we performed a covariance analysis using the Day 1 values as covariates; the inter-group 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 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 (Fig. 1). The results of the subscores by acid reflux-related symptom and motor deficiency symptom are

shown in Tables 6 and 7, respectively. The comparison of the amount of variation in the FSSG subscores 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 subscores were higher in the VPZ group than those in the PPI group at each time point (Figs 2 and 3).

Next, we examined the GSRS total scores/subscores and the HADS scores; between Day 1 and each time point, there was no significant difference in the amount of variations in 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 (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 an upward tendency over time from approximately 15% to 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 maintenance 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. 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 (Table 1). Therefore, we tried to compare the two groups, although this was not an endpoint set in the protocol. Among the patient backgrounds, statistically significant inter-group 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 [28-30]. 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 subscores (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). This result may be attributable to the smaller number of patients, but there is possibility that the factors examined do not have a strong association with GERD relapse during withdrawal. Thus, patients with certain backgrounds are not more prone to relapse; suggesting that there is little need to take the patient backgrounds into account in drug discontinuation.

There was no statistically significant inter-group 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% (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 [31] describes that PPIs have little causality with adverse events including renal impairment, dementia. We previously reported that the effect of VPZ is considerably stronger than the 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. This is consistent with the result that VPZ had shorter blood half-life of 7.7 hr than that in the stomach where VPZ remains as unchanged drug for a longer time because it was inactivated by acid [32]. There are no reports on serious side effects of VPZ for up to two years [33], but elucidation of the safety of VPZ in long-term maintenance therapy is important. This study show that there was no significant inter-group 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, 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 [30].

There is a report [34] affirming the acid hypersecretion by ASID discontinuation, but several articles [35-37] reporting 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, and (3) endoscopy was not performed after the drug withdrawal.

Conclusion

There were no patient factors to be considered 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 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.

Abbreviations

Abbreviation	Meaning of abbreviation
ASID	Acid-secretion inhibition drug
BMI	Body mass index
CYP	Cytochrome P450
FSSG	Frequency scale for the symptoms of gastroesophageal reflux disease (GERD)
eGERD	Erosive gastroesophageal reflux disease
GERD	Gastroesophageal reflux disease
GSRS	Gastrointestinal symptom rating scale
HADS	Hospital anxiety and depression scale
LA	Los Angels
P-CAB	Potassium-competitive acid blocker
PPI	Proton pump inhibitor
VPZ	Vonoprazan

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committees of each institution for human research, based on the Declaration of Helsinki and the Japanese Guidance on Clinical Trials.

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

Takeuchi T: Preparation, reviewing, and edition of this paper, performing data curation and formal analysis, and supervising methodology and visualization. Tanaka H, Nishida S, Hongo H, Takii M, Higashino T, Sanomura M, Miyazaki H, Hoshimoto M, Kimura T, Sakaguchi M, Abe T, Hakoda A, Sugawara N, Iwatsubo T, Kawaguchi S, Ota K and Kojima Y: Investigation, Resources. Higuchi K: Preparation, reviewing, and edition of this paper, Study supervision.

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Tables

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

Factor	Item	Mean ± SD	Min-Med-Max	P value
Patient background	Sex: male (%)/female (%)	No. of subjects		0.036[a]
	Entire population (n=93)	55 (59.1%)/38(40.9%)		
	PPI (n=47)	33 (70.2%)/14 (29.8%)		
	VPZ (n=46)	22 (47.8%)/24 (52.2%)		
	Age (year)	64.8±13.7	25.0-68.0-93.0	0.067[b]
	Entire population (n=93)	67.4±11.4	40.0-70.0-93.0	
	PPI (n=47)	62.2±15.4	25.0-68.0-79.0	
	VPZ (n=46)			
	Height (cm)	161.78±9.04	140.00-162.00-183.00	0.103[b]
	Entire population (n=93)	163.30±9.03		
	PPI (n=47)	160.24±8.88	145.00-163.50-180.00	
	VPZ (n=46)		140.00-160.00-183.00	
	Weight (kg)	62.94±11.41	35.20-63.00-106.00	0.598[b]
	Entire population (n=93)	62.31±10.49	35.20-63.00-83.00	
	PPI (n=47)	63.57±12.37	46.30-62.25-106.00	
	VPZ (n=46)			
	BMI (kg/m^2)	23.96±3.38	16.20-23.80-41.00	0.048[b]
	Entire population (n=93)	23.28±2.89	16.20-23.20-29.10	
	PPI (n=47)	24.66±3.71	19.30-24.45-41.00	
	VPZ (n=46)			
	Blood gastrin (pg/mL)	587.2±510.0	10.0-455.0-2500	<0.001[b]
	Entire population (n=92)	383.3±281.7	10.0-280.0-1300	
	PPI (n=47)	800.3±603.5	69.0-620.0-2500	
	VPZ (n=45)			
	Blood pepsinogen I (ng/mL)	173.07±159.68	24.10-135.50-1040.00	0.005[b]
	Entire population (n=92)	127.96±70.14	24.10-120.00-285.00	
	PPI (n=47)	220.20±207.71	25.30-153.00-1040.00	
	VPZ (n=45)			

Blood pepsinogen II (ng/mL)	31.47±29.76	4.70-22.35-173.00	<0.001[b]
Entire population (n=92)	20.84±10.71	4.70-19.30-52.40	
PPI (n=47)	42.58±38.27	7.30-30.80-173.00	
VPZ (n=45)			
Pepsinogen I/II ratio	5.71±1.70	1.50-5.60-10.00	0.008[b]
Entire population (n=92)	6.17±1.84	2.70-6.10-10.00	
PPI (n=47)	5.24±1.40	1.50-5.40-9.60	
VPZ (n=45)			
Smoking habit: Yes/No	No. of subjects		1.000[a]
Entire population (n=92)	20 (21.7%)/72 (78.3%)		
PPI (n=47)	10 (21.3%)/37 (78.7%)		
VPZ (n=45)	10 (22.2%)/35 (77.8%)		
Alcohol drinking: Yes/No	No. of subjects		0.670[a]
Entire population (n=92)	56 (60.9%)/36 (39.1%)		
PPI (n=47)	30 (63.8%)/17 (36.2%)		
VPZ (n=45)	26 (57.8%)/19 (42.2%)		

*: Comparison between conventional PPI and VPZ dose groups, [a]: Fishers' exact probability test, [b]: Unpaired t-test, Day 1: starting day of drug discontinuation, GERD: gastroesophageal reflux disease, LA: Los Angeles, Max: maximum, Med: median, Min: minimum, No.: No. of patients, PPI: proton pump inhibitor, SD: Standard deviation, VPZ: vonoprazan

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

Factor	Item	Mean ± SD	Min-Med-Max	P value
Patient background	Sex: male (%)/female (%)	No. of subjects		0.640[a]
	Entire population (n=92)	54 (58.7%)/38 (58.7%)		
	FSSG<8 (n=66)	40 (60.6%)/26 (39.4%)		
	FSSG≥8 (n=26)	14 (53.8%)/12 (46.2%)		
	Age (year)	64.1±13.8	25.0-68.0-93.0	0.499[b]
	Entire population (n=92)	66.3±13.6	31.0-70.5-83.0	
	FSSG<8 (n=66)			
	FSSG≥8 (n=26)			
	Height (cm)	162.30±9.72	140.00-163.05-183.00	0.433[b]
	Entire population (n=92)	160.65±7.19		
	FSSG<8 (n=66)		147.00-160.65-174.00	
	FFSSG≥8 (n=26)			
	Weight (kg)	63.36±11.97	46.30-62.00-106.00	0.613[b]
	Entire population (n=92)	62.01±10.24	16.20-64.20-29.30	
	FSSG<8 (n=66)			
	FSSG≥8 (n=25)			
	BMI (kg/m^2)	23.97±3.49	18.60-23.70-41.00	0.958[b]
	Entire population (n=92)	23.93±3.22	19.30-24.35-41.00	
	FSSG<8 (n=66)			
	FSSG≥8 (n=26)			
	Blood gastrin (pg/mL)	575.0±534.6	10.0-430.0-2500.0	0.770[b]
	Entire population (n=91)	610.5±457.4	83.0-490.0-1600.0	
	FSSG<8 (n=66)			
	FSSG≥8 (n=25)			
	Blood pepsinogen I (ng/mL)	174.74±176.09	24.10-135.50-1040.00	0.897[b]
	Entire population (n=91)	169.83±112.43	41.70-129.00-555.00	
	FSSG<8 (n=66)			
	FSSG≥8 (n=25)			

	Blood pepsinogen II (ng/mL) Entire population (n=91) FSSG<8 (n=66) FSSG≥8 (n=25)	32.21±33.45 28.68±17.33	4.70-21.55-173.00 9.40-22.40-76.50	0.618[b]
	Pepsinogen I/II ratio Entire population (n=91) FSSG<8 (n=66) FSSG≥8 (n=25)	No. of subject 5.66±1.75 5.97±1.49	1.50-5.65-10.00 3.00-5.60-9.60	0.443[b]
	Smoking habit: Yes/No Entire population (n=91) FSSG<8 (n=65) FSSG≥8 (n=26)	No. of subjects 15 (23.1%)/50 (76.9%) 5 (19.2%)/21 (80.8%)		0.785[a]
	Alcohol drinking (No.): Yes/No Entire population (n=91) FSSG<8 (n=65) FSSG≥8 (n=26)	No. of subjects 38 (58.5%)/27 (41.5%) 17 (65.4%)/9 (34.6%)		0.638[a]

*: Comparison between groups with FSSG<8 and FSSG≥8, [a]: Fishers' exact probability test, [b]: Unpaired t-test, 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.: No. of patients, SD: Standard deviation, Week 4: At 4 weeks from the starting day of drug withdrawal

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	10-455-2500	10-97.5-1500	-2416- -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	10-280-1300	10-95.5-970	-1190- -176.5-290	
VPZ dose group[c]	Mean ± SD	800.27±603.48	163.39±221.22	-636.13±616.13	<0.0001
	Min-Med-Max	69-620-2500	46-99-1500	-2416- -470-500	

*: Comparison between Day 1 and Week 4 by using paired t-test, [a]: n=92 but n=91 for variation because of 1 missing value on Day and at Week4, [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, Day1: 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, variation: values obtained by subtracting the values on Day 1 from those at Week 4

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 - 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*	P-value**
PPI + VPZ dose groups					
Day 1	93	2.2±2.3	0-2-7		
Week 1	93	4.8±5.5	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	-
PPI vs. VPZ dose group					
Day 1					
Week 1				-	0.1060
Week 2				-	0.1643
Week 3				-	0.2264
Week 4				-	0.2522

*: Comparison of the values at each week with those on Day 1 determined by paired t-test, **: Inter-group comparison by unpaired t-test, FSSG: Frequency Scale for the Symptom of Gastroesophageal Reflux Disease, Max: maximum, Med: median, Min: minimum, PPI: proton pump inhibitor, SD: Standard deviation, VPZ: vonoprazan

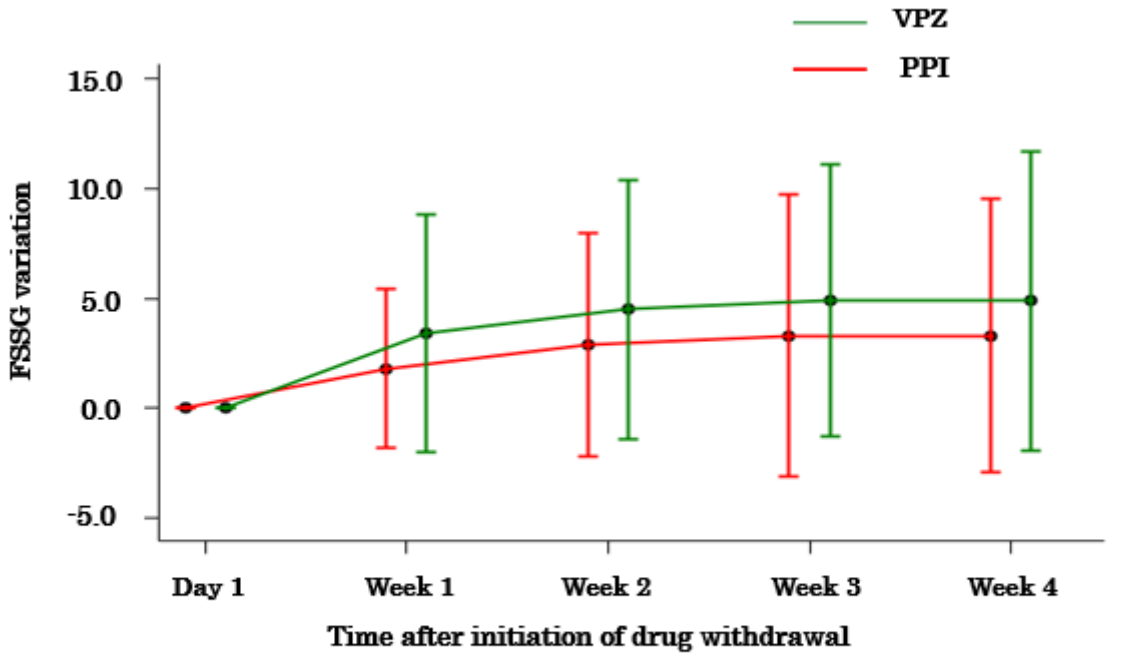
Table 6 Change of FSSG sub-score related to acid reflux

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
*: Comparison of the values at each week with those on Day 1 determined by paired t-test, FSSG: Frequency Scale for the Symptom of Gastroesophageal Reflux Disease, Max: maximum, Med: median, Min: minimum, PPI: proton pump inhibitor, SD: Standard deviation, VPZ: vonoprazan				

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

*: Comparison of the values at each week with those on Day 1 determined by paired t-test, FSSG: Frequency Scale for the Symptom of Gastroesophageal Reflux Disease, Max: maximum, Med: median, Min: minimum, PPI: proton pump inhibitor, SD: Standard deviation, VPZ: vonoprazan

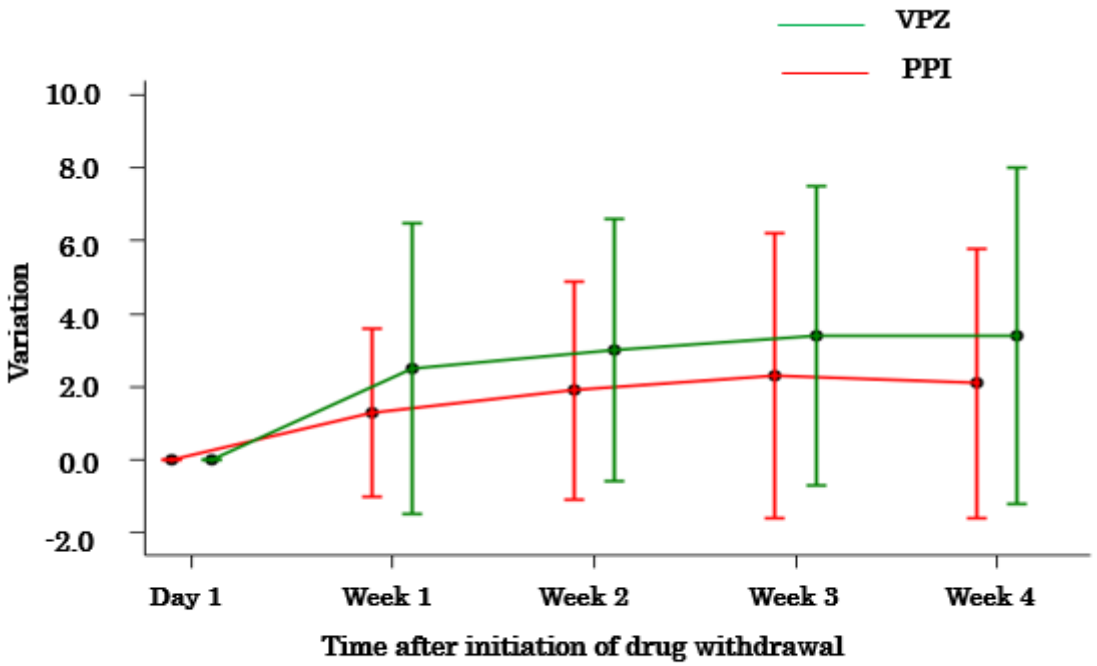
Figures



No. of patients: 46 to 47 in PPI dose group, 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

Figure 1

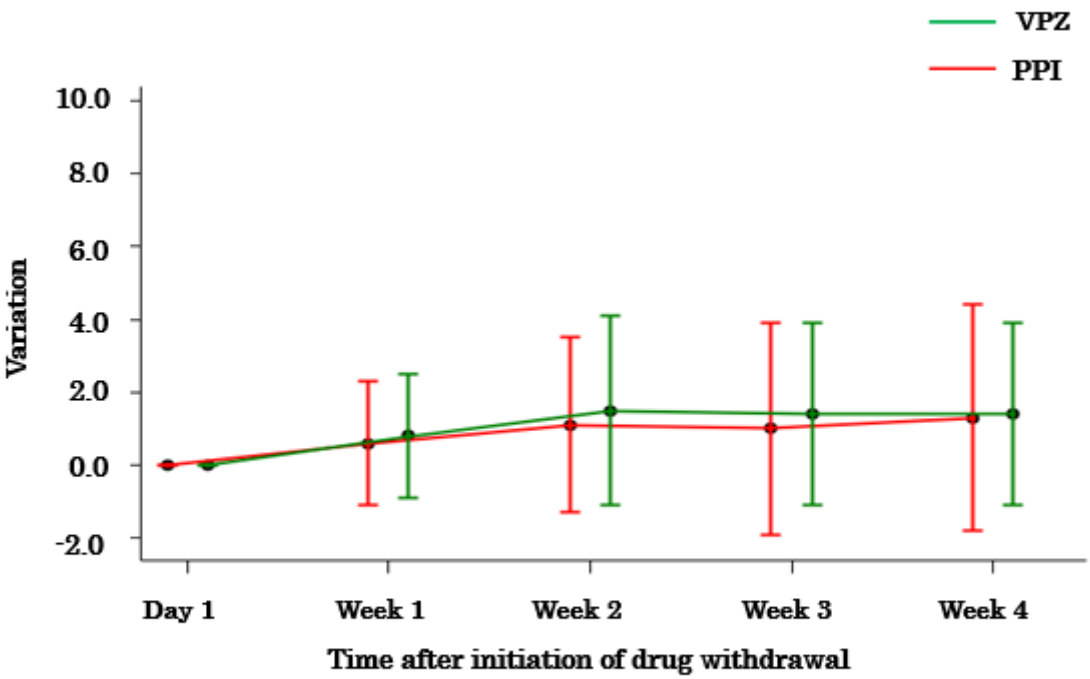
Change of variation of FSSG total score from Day 1



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

Figure 2

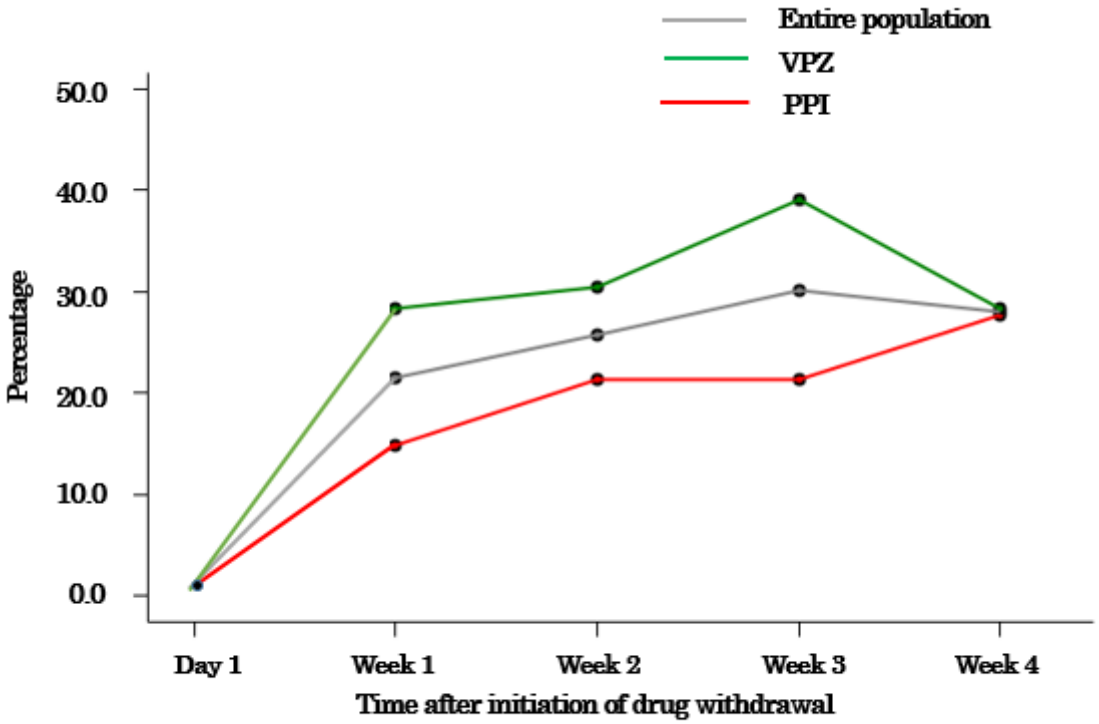
Change of variation of FSSG sub-score related to acid reflux from Day 1



No. of patients: 46 to 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

Figure 3

Change of variation of FSSG sub-score related to dysmotility from Day 1



No. of patients: 46 to 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

Figure 4

Percentage of patients showing FSSG total score of 8 or higher at each time point

Supplementary Files

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- EJMRupplementaryfile220114.docx