

[ORIGINAL ARTICLE]

Efficacy of Vonoprazan for Gastroesophageal Reflux Symptoms in Patients with Proton Pump Inhibitor-resistant Non-erosive Reflux Disease

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Abstract:

Objective Clinically, patients with proton pump inhibitor (PPI)-resistant gastroesophageal reflux disease (GERD) are very challenging to treat. The aim of this study was to determine the rates of symptom relief and adverse events among PPI-resistant GERD patients that changed their therapy from a PPI to vonoprazan.

Methods Patients with severe gastroesophageal reflux symptoms (total GERD-Q score ≥ 8) without endoscopic findings of mucosal breaks who changed their medication from a PPI to vonoprazan during a 12-week period from 2015 to 2016 at 2 hospitals were selected. The primary outcome was the self-reported relief of gastroesophageal reflux symptoms. The odds ratio (OR) for the improvement of symptoms was calculated based on an exact binomial distribution using a matched-pair analysis. The secondary outcome was the GERD-Q score and adverse events.

Results Twenty-six patients (6 men) with a mean age of 67.5 years were analyzed. After the therapy was changed from a PPI to vonoprazan, 18 patients (69.2%) reported an improvement, 6 (23.1%) reported no change, and 2 (7.7%) reported an exacerbation of symptoms. A change in therapy was significantly associated with improved self-reported symptoms (OR 9.0, $p < 0.001$). The mean total GERD-Q score during vonoprazan treatment was significantly lower than that during PPI therapy (11.96 vs. 8.92). There were no significant differences in the incidence of adverse events between the therapies.

Conclusion Changing the medication from a PPI to vonoprazan was significantly associated with an improvement in gastroesophageal reflux symptoms. Vonoprazan is one of the most promising treatment options for patients with PPI-resistant GERD.

Key words: proton pump inhibitor, NERD, vonoprazan, gastroesophageal reflux symptoms, GERD-Q

(Intern Med 57: 2443-2450, 2018)

(DOI: 10.2169/internalmedicine.0492-17)

Introduction

Gastroesophageal reflux disease (GERD) is a common disease encountered in daily clinical practice. The prevalence of GERD in Japan is approximately 10%, which is similar to the prevalence in Western countries (1), and is increasing (2). More than half of GERD cases in Japan show

normal esophageal mucosa on endoscopy, which is known as non-erosive reflux disease (NERD) (3). Proton pump inhibitors (PPIs) are the primary treatment option for GERD and NERD and provide superior symptom relief and mucosal healing to other drugs, such as histamine H₂-receptor antagonists and mucoprotective agents (4, 5). As such, PPIs are recommended as first-line drugs for patients with GERD and NERD (3).

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Received: November 7, 2017; Accepted: January 24, 2018; Advance Publication by J-STAGE: March 30, 2018

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However, an important clinical issue is that a subgroup of GERD patients does not have satisfactory improvement, even after PPI therapy. In particular, NERD patients are less sensitive to PPI treatment than reflux esophagitis patients (6, 7). Several medical (8, 9), surgical (10, 11), and endoscopic (12) approaches have been performed as treatments for NERD, but no therapy other than PPI treatment is currently recommended for NERD patients (3). Changing the type of PPI and the addition of other medications have been proposed (8, 9), but the evidence for these strategies is limited. Therefore, another effective pharmacological approach is urgently required for the management of NERD.

Recently, vonoprazan, a new agent for gastric acid suppression, has been used as a treatment option for GERD in Japan (13). Vonoprazan is an active acid blocker that inhibits the proton pump activity of cytoplasmic tubulovesicles and secretory canaliculus, leading to the strong inhibition of acid production compared to conventional PPIs (14, 15). Its efficacy for endoscopic erosive esophagitis was reported in a multicenter randomized controlled trial; vonoprazan showed non-inferiority to lansoprazole for mucosal healing (13). Another observational study reported that vonoprazan is effective in treating PPI-resistant reflux esophagitis (16). However, its efficacy for treating GERD symptoms, especially in NERD patients, is not well defined.

Given the strong acid-inhibition effects of vonoprazan, we hypothesized that it would improve the gastroesophageal reflux symptoms in patients with NERD. We performed a preliminary study to evaluate the effects of changing the medication from a PPI to vonoprazan. The aims of this study were to elucidate the rates of symptom relief and adverse events after changing therapy from a PPI to vonoprazan in NERD and PPI-resistant NERD patients and to identify factors that predict symptom relief among NERD patients taking vonoprazan.

Materials and Methods

Study design and setting

We performed a retrospective self-controlled study from 2015 to 2017 at the Graduate School of Medicine, the University of Tokyo, and the Japan Association for Development of Community Medicine, Nerimahikarigaoka Hospital.

We were interested in the effects of changing the therapy from a PPI to vonoprazan in patients with NERD. Because almost all patients with persistent refractory NERD had changed their therapy from a PPI to vonoprazan at our hospitals, we were unable to define a suitable control group to evaluate the effects of the therapy change. Therefore, we selected a self-controlled design to compare gastroesophageal reflux symptoms before and after the therapy change in the same patients.

Participants

We selected outpatients ≥ 18 years of age with persistent

severe gastroesophageal reflux symptoms (total GERD-Q score ≥ 8) without endoscopic findings of mucosal breaks on an upper gastrointestinal endoscopy examination performed before the initial PPI treatment and who changed their therapy from a PPI to vonoprazan. PPI-resistant NERD was defined as a condition in which reflux symptoms were not sufficiently mitigated (total GERD-Q score ≥ 8) even after the oral administration of a PPI at a standard or double dose for 8 weeks (17-20). This study was approved by the institutional review board of the University of Tokyo (No. 2058).

The evaluation of GERD symptoms and the effects of switching from a PPI to vonoprazan

Patients had their first evaluation for gastroesophageal reflux symptoms using the GERD-Q questionnaire when they were administered PPIs before the therapy change to vonoprazan. After obtaining consent, physicians changed the medication to vonoprazan at the same titer dose as the PPI for four weeks (wash-out period). The patients then continued to take vonoprazan for an additional eight weeks (observation period). After 12 weeks of taking vonoprazan, physicians performed interviews and administered the GERD-Q questionnaire again to assess the gastroesophageal reflux symptoms in patients (Figure).

GERD-Q score

The GERD-Q is a self-reported questionnaire developed to diagnose GERD (21). It consists of six items rated on a 4-point scale (0 points, no symptoms; 1 point, 1 day; 2 points, 2-3 days; and 3 points, 4-7 days of symptoms for items 1, 2, 5, and 6; and 3 points, no symptoms; 2 points, 1 day; 1 point, 2-3 days; and 0 points, 4-7 days of symptoms for items 3 and 4), and patients are asked to reflect on their symptoms over the preceding week. The questionnaire has been validated in multiple languages, including Japanese (Supplementary material 1) (22-24).

Outcomes and variables

The primary outcome was the proportion of self-reported relief of gastroesophageal reflux symptoms eight weeks after the washout period (physician question: How have your gastroesophageal reflux symptoms changed? Patient response: improvement, no change, or exacerbation) (25). The secondary outcome was the total GERD-Q score (heart burn, regurgitation, pain in the upper stomach, nausea, difficulty getting a good night's sleep, and need for additional medication). We also evaluated the following adverse events as identified in an interview conducted by a physician: upper respiratory tract infection, constipation, diarrhea, nausea, liver damage, and rash.

We evaluated the known risk factors for acid reflux, such as the age, sex, body mass index (BMI), alcohol consumption, smoking, medication, *Helicobacter pylori* infection, and upper gastrointestinal endoscopic findings (3, 26). Hiatal hernia was defined as an apparent separation of the esophagogastric junction and diaphragm impression by >2

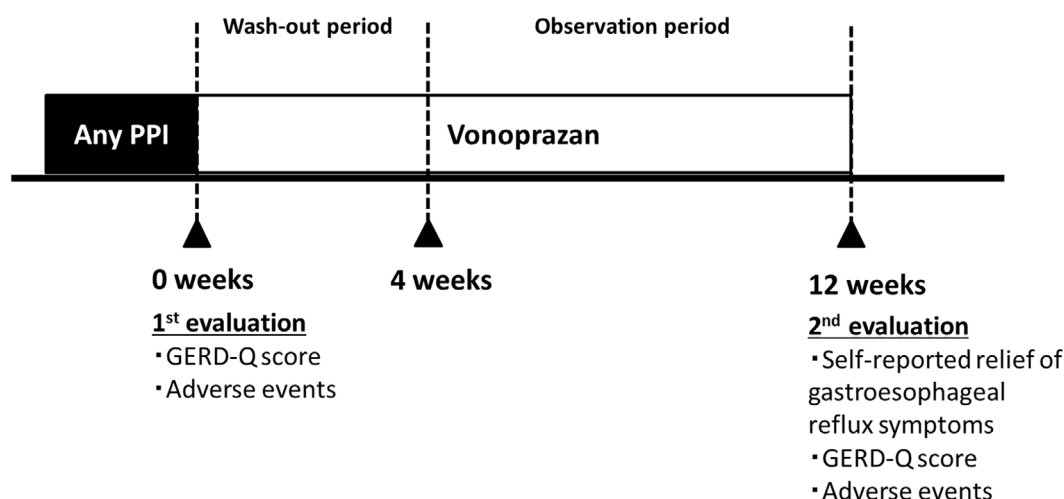


Figure. The evaluation of GERD symptoms and changing medication from a PPI to vonoprazan.

cm, and endoscopic gastric mucosal atrophy (27) was evaluated according to the Kimura-Takemoto classification. *H. pylori* infection was evaluated using serological testing, a urea breath test, or a stool antigen test. Physician interviews and endoscopic findings based on the Kyoto classification of gastritis were also employed to evaluate post-eradication gastritis (28). We also assessed the medications used, including the type and duration of pretreatment PPIs (lansoprazole, omeprazole, rabeprazole, and esomeprazole); the concomitant use of other drugs [e.g. histamine 2 receptor antagonists, mucoprotective agents, low-dose aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs)], anticoagulants (e.g. warfarin), and non-vitamin K antagonist oral anticoagulants (NOACs; e.g. dabigatran, rivaroxaban, edoxaban, and thienopyridine); and the adherence to the PPI and vonoprazan treatment.

Statistical analyses

We calculated the proportion of self-reported relief of gastroesophageal reflux symptoms after eight weeks (observation period). The odds ratio (OR) and 95% confidence interval (CI) for the improvement of symptoms (improvement vs. exacerbation) were calculated based on exact binomial distributions using matched-pair analyses. Because the observations before and after the therapy change for each patient were treated as matched pairs, patients with no change in symptoms did not contribute to the OR calculation (29). In addition, we also compared the GERD-Q scores, as well as the occurrence of adverse events during PPI and vonoprazan therapy, using paired t-tests and the exact matched-pair method.

In the subgroup analysis, we calculated the proportion of self-reported relief of gastroesophageal reflux symptoms and the OR for improvement of symptoms in patients with PPI-resistant NERD according to the *H. pylori* infection status (infected, uninfected, or eradicated).

Logistic regression analyses were performed to identify the factors associated with an improvement in gastroe-

sophageal reflux symptoms when patients received vonoprazan. A p value <0.05 was considered statistically significant. All statistical analyses were performed using the SAS software program, ver. 9.4 (SAS Institute, Cary, USA).

Results

A total of 26 eligible patients were analyzed. The baseline patient characteristics are shown in Table 1. The mean age was 67.5 years, and 7 (26.9%) patients were men. The rate of *H. pylori* persistent infection was 15.4% (n=4). Prior to the medication change, PPIs of rabeprazole, lansoprazole, omeprazole, and esomeprazole were administered to 11, 6, 1, and 8 patients, respectively. The mean duration of PPI therapy was 136 weeks.

Of the patients who underwent vonoprazan therapy, 15 (57.7%) received 20 mg/day, and the remaining 11 (42.3%) received 10 mg/day. No significant differences in the mean adherence were found between patients who received a PPI (95.1%) and those who received vonoprazan (89.8%) (p=0.384). The responses for self-reported relief of symptoms were "improvement" in 18 patients (69.2%), "no change" in 6 (23.1%), and "exacerbation" in 2 (7.7%). Of the 18 patients with symptom improvement, 9 received vonoprazan 10 mg/day, and 9 received vonoprazan 20 mg/day. Changing therapy was significantly associated with an improvement in self-reported symptoms (OR 9.0, 95% CI 2.2-80.3, p<0.001) (Table 2). Vonoprazan significantly decreased the incidence of reflux-related symptoms, as shown by a decrease in the mean total GERD-Q score (from 11.96 to 8.92, p<0.001). In addition, the GERD-Q heartburn, regurgitation, and insomnia scores were significantly lower in patients on vonoprazan therapy than in those on PPIs (Table 3).

Among these NERD patients, 19 received standard or double PPI doses and were therefore categorized as having PPI-resistant NERD. In the PPI-resistant NERD patients, the responses for self-reported symptom relief were "improvement" in 12 patients (63.2%), "no change" in 5 (26.3%),

and “exacerbation” in 2 (10.5%). Changing therapy was significantly associated with an improvement in self-reported symptoms (OR 6.0, 95% CI 1.3-55.2, $p=0.013$) (Table 2) and a decrease in the mean total GERD-Q score (from 12.21

to 9.37, $p<0.001$) (Table 3).

The therapeutic responses according to the *H. pylori* infection status (infected, uninfected and eradicated) are shown in Supplementary material 2 and 3. Treatment with vonoprazan was significantly associated with an improvement in self-reported symptoms and in the mean total GERD-Q score, regardless of the *H. pylori* status.

The results of univariate analyses of predictive factors leading to an improvement in reflux symptoms are shown in Table 4. No significant associations were found between symptom relief and these factors, including the BMI, smoking, endoscopic findings, and *H. pylori* status.

Adverse events during PPI and vonoprazan therapy are shown in Table 5. No significant differences in the rate of adverse events were found between treatment periods. Only one case had a new adverse event (rash) during vonoprazan therapy. Other adverse events, such as upper respiratory tract infection and diarrhea, were observed in the same patients during both PPI and vonoprazan therapy.

Discussion

We found that changing therapy from a PPI to vonoprazan was associated with an improvement in gastroesophageal reflux symptoms in patients with NERD and PPI-resistant NERD. No significant differences were found in the rate of adverse events between patients receiving PPIs and those receiving vonoprazan therapy.

Vonoprazan is the only potassium-competitive acid blocker available for clinical use. It was developed to overcome the shortcomings of PPIs, such as the short half-life, insufficient acid suppression, slow onset of action, and metabolic variation (30). Vonoprazan causes effective acid suppression by strongly inhibiting the H-K ATPase activity of parietal cells; this has led to superior clinical results against various acid-related diseases (31-33). Regarding GERD, a previous study investigated the efficacy of vonoprazan on esophageal mucosal healing (13). Ashida et al. reported that 99% of patients with erosive esophagitis had mucosal heal-

Table 1. Baseline Patient Characteristics (n=26).

Variable	n (%)
Age, mean±SD	67.5±12.2*
Sex, male	7 (26.9)
BMI, mean±SD	22.3±2.9*
Current alcohol consumption	6 (23.1)
Current smoker	1 (3.9)
Medication	
Pre-treatment PPI	
Rabeprazole, 10 mg/day	5 (19.2)
Rabeprazole, 20 mg/day	6 (23.0)
Lansoprazole, 15 mg/day	5 (19.2)
Lansoprazole, 30 mg/day	1 (3.9)
Omeprazole, 10 mg/day	1 (3.9)
Omeprazole, 20 mg/day	0 (0.0)
Esomeprazole, 10 mg/day	1 (3.9)
Esomeprazole, 20 mg/day	7 (26.9)
Concomitant drug use	
Histamine 2 receptor antagonists	0 (0.0)
Mucoprotective agents	7 (26.9)
Low-dose aspirin	3 (11.5)
NSAIDs	5 (19.2)
Anticoagulants	2 (7.7)
Thienopyridine	1 (3.9)
Endoscopic findings	
Hiatus hernia	7 (28.0)
Endoscopic gastric mucosal atrophy	13 (50.0)
<i>H. pylori</i> status	
Persistent infection	4 (15.4)
Eradicated	9 (34.6)
Uninfected	13 (50.0)

BMI: body mass index, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor, SD: standard deviation

*Mean

Table 2. Self-reported Relief of Gastroesophageal Reflux Symptoms after Switching from a PPI to Vonoprazan.

Outcome	Number of patients (%)	Odds ratio (95% CI)	p value
NERD (n=26)			
Self-reported relief of symptoms			
Improvement	18 (69.2)	9.0 (2.2-80.3)	<0.001
No change	6 (23.1)		
Exacerbation	2 (7.7)		
PPI-resistant NERD (n=19)			
Self-reported relief of symptoms			
Improvement	12 (63.2)	6.0 (1.3-55.2)	0.013
No change	5 (26.3)		
Exacerbation	2 (10.5)		

NERD: reflux esophagitis and non-erosive reflux disease, CI: confidence interval, PPI: proton pump inhibitor
Bolding indicates statistical significance ($p<0.05$).

Table 3. GERD-Q Score during PPI and Vonoprazan Therapy.

Outcome	PPI	Vonoprazan	Change (95% CI)	p value
NERD (n=26)				
GERD-Q	Mean score±SD	Mean score±SD		
Total	11.96±1.89	8.92±2.61	-3.04 (-4.02 to -2.05)	<0.001
Heartburn	2.27±1.04	1.23±1.14	-1.04 (-1.56 to -0.52)	<0.001
Regurgitation	1.73±1.04	1.11±1.07	-0.62 (-1.03 to -0.20)	0.005
Pain	2.58±0.50	2.50±0.51	-0.08 (-0.30 to 0.15)	0.490
Nausea	2.50±0.51	2.77±0.43	0.27 (-0.00009 to 0.54)	0.050
Insomnia	2.15±1.05	0.92±1.09	-1.23 (-1.76 to -0.70)	<0.001
Additional medication	0.73±1.12	0.38±0.80	-0.35 (-0.79 to 0.10)	0.119
PPI-resistant NERD (n=19)				
GERD-Q	Mean score±SD	Mean score±SD		
Total	12.21±1.93	9.37±2.73	-2.84 (-4.13 to -1.55)	<0.001
Heartburn	2.42±0.90	1.37±1.11	-1.05 (-1.66 to -0.44)	0.002
Regurgitation	1.84±0.96	1.32±1.11	-0.53 (-0.93 to -0.12)	0.014
Pain	2.58±0.51	2.47±0.51	-0.11 (-0.38 to 0.17)	0.429
Nausea	2.53±0.51	2.68±0.48	0.16 (-0.18 to 0.49)	0.331
Insomnia	2.11±1.05	1.05±1.13	-1.05 (-1.70 to -0.40)	0.003
Additional medication	0.74±1.10	0.47±0.90	-0.26 (-0.79 to 0.27)	0.310

NERD: non-erosive reflux disease, CI: confidence interval, PPI: proton pump inhibitor, SD: standard deviation
 Bolding indicates statistical significance (p<0.05).

Table 4. Factors Associated with an Improvement in the Gastroesophageal Reflux Symptoms after Changing Therapy (n=26).

Variable	Improved/Not improved	OR (95% CI)	p value
Age, years	68.6/65.0*	1.03 (0.96-1.10)	0.481
Sex, male	5/2	1.15 (0.17-7.74)	0.883
BMI, kg/m ²	22.4/22.0*	1.04 (0.78-1.40)	0.787
Current alcohol consumption	5/1	2.69 (0.26-27.8)	0.406
Current smoker	0/1	NA	NA
Pre-treatment PPI			
Rabeprazole	8/3	1.33 (0.24-7.35)	0.741
Lansoprazole	4/2	0.86 (0.12-6.01)	0.877
Omeprazole	1/0	NA	NA
Esomeprazole	5/3	0.64 (0.11-3.74)	0.621
Concomitant drug use			
Histamine 2 receptor antagonists	0/0	NA	NA
Mucoprotective agents	5/2	1.15 (0.17-7.74)	0.883
Low-dose aspirin	2/1	0.88 (0.07-11.3)	0.919
NSAIDs	2/3	0.21 (0.03-1.62)	0.134
Anticoagulants	2/0	NA	NA
Thienopyridine	1/0	NA	NA
Vonoprazan adherence (%)	88.6/93.4*	0.97 (0.89-1.07)	0.540
Endoscopic findings			
Hiatus hernia	5/2	1.25 (0.19-8.44)	0.819
Endoscopic gastric mucosal atrophy	8/5	0.48 (0.09-2.65)	0.399
<i>H. pylori</i> status			
Uninfected or eradicated	10/3	1.00	
Persistent infected	8/5	0.48 (0.09-2.65)	0.399

BMI: body mass index, CI: confidence interval, NA: not applicable, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio, PPI: proton pump inhibitor

*Mean

Table 5. Adverse Events during PPI and Vonoprazan Therapy (n=26).

AE	Number of patients with AE			p value
	Both PPI and vono	PPI only	Vono only	
Upper respiratory tract infection	4	1	0	1.000
Constipation	0	1	0	1.000
Diarrhea	2	1	0	1.000
Nausea	0	1	0	1.000
Rash	1	3	1	0.250

AE: adverse event, NA: not applicable, PPI: proton pump inhibitor, vono: vonoprazan

ing after 8 weeks of vonoprazan therapy (13). This trial showed no inferiority over lansoprazole in mucosal healing, and some subgroup analyses even showed that vonoprazan was superior to lansoprazole. However, clinical data indicating that vonoprazan leads to an improvement in NERD symptoms are very limited.

In this self-controlled study, we found that switching from a PPI to vonoprazan for 12 weeks significantly improved gastroesophageal reflux symptoms in patients with NERD, including PPI-resistant NERD. Our results validate the efficacy of vonoprazan for treating GERD not only in erosive esophagitis but also in NERD patients. Our results are consistent with those of a recent retrospective observational study that reported an improvement in GERD symptoms in NERD patients treated with vonoprazan for 4 weeks (34).

Several factors may explain the effectiveness of vonoprazan. First, it has a strong acid-inhibition effect. A pharmacological study on healthy adults showed that patients treated with vonoprazan had a significantly longer pH 4 holding time than those treated with conventional PPIs (35). In addition, once-daily vonoprazan led to sustained acid suppression, which resulted in an excellent nighttime pH 4 holding time ratio. This might reduce nocturnal acid breakthrough, which is often associated with refractory symptoms of GERD (3). Second, due to the open-label non-randomized design of our study, the placebo effect may have been associated with improved clinical outcomes.

Previous observational studies have evaluated the pathogenesis of PPI-resistant NERD and reported that 10-30% of PPI-resistant NERD patients had acid-related reflux (17, 20). In the present study, we showed that vonoprazan improved symptoms even in PPI-resistant NERD patients. However, two patients experienced an exacerbation of symptoms after vonoprazan treatment, although this may have been due to other causal factors, such as non-acid reflux and esophageal motility disorder (17, 20).

The results of our study suggest a new treatment option for patients with NERD. We found that vonoprazan improved gastroesophageal reflux symptoms in 69.2% of NERD and 63.2% of PPI-resistant NERD patients. This rate is higher than that achieved by studies that escalated the dose of PPI (36), co-administered a prokinetic drug (37, 38), and treated patients with Japanese herbal medicine (39). In our study, after 12 weeks of vonoprazan and PPI therapy,

there were no marked differences in the rate of adverse events reported by patients, suggesting the safety of vonoprazan therapy. However, short-term (four weeks) vonoprazan therapy in a recent trial failed to improve GERD symptoms in NERD patients (40). Thus, a large-scale prospective study is required to confirm the effects of long-term vonoprazan treatment for PPI-resistant NERD.

Our study had several strengths. First, this is the first study to show the efficacy of vonoprazan for both NERD and PPI-resistant NERD. Second, we performed upper endoscopy to exclude non-GERD gastrointestinal diseases, such as peptic ulcers and malignancies. Studies that are based only on a questionnaire assessment do not exclude these diseases. Third, using a self-controlled design that included patient data from different time periods, study participants acted as their own controls; as such, the confounding effects of risk factors that are generally time-invariant were theoretically minimized. Therefore, the estimated effects of changing therapy were less likely to be biased by time-invariant factors, such as sex, the BMI, genetic factors, and the medical history, although our sample size was relatively small (41).

However, our study also had several limitations. First, we used a retrospective, open-label, non-randomized, controlled design, which has several biases. Second, because the sample size was small, the statistical power might have been insufficient to adjust for time-varying confounders, such as transient concomitant medication use and transient physical activity. Third, CYP2C19 genotyping and pH monitoring were not performed in our patients.

In conclusion, switching from a PPI to vonoprazan was significantly associated with an improvement in gastroesophageal reflux symptoms in patients with NERD and PPI-resistant NERD without an increase in adverse events. Therefore, vonoprazan represents a promising treatment option for patients with NERD and PPI-resistant NERD.

The institutional review board of the University of Tokyo approved this study.

Author's disclosure of potential Conflicts of Interest (COI).

Mitsuhiro Fujishiro: Research funding, Hoya and Pentax.

Financial Support

This work was supported by grants from the KAKENHI Grant-in-Aid for Scientific Research, 17K15928 (R.N).

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