Efficacy of vonoprazan, a novel potassium-competitive acid blocker, in patients with proton pump inhibitor-refractory acid reflux

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Short title: Vonoprazan in PPI-refractory GERD

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1. Abstract

Background: Vonoprazan (VPZ), a novel potassium-competitive acid blocker, has been reported to produce a more rapid and profound gastric acid suppression than standard proton pump inhibitors (PPIs) in healthy volunteers and in patients with reflux disease.

Objective: We evaluated the efficacy of VPZ in patients with PPI-refractory gastroesophageal reflux disease (GERD) who exhibited continued pathological esophageal acid exposure.

Methods: Despite ≥8 weeks of appropriate PPI therapy, patients with persistent reflux symptoms and pathological esophageal acid exposure (EAE) times (EAETs ≥4%), documented by baseline multichannel intraluminal impedance-pH (MII-pH) monitoring between November 2012 and September 2016, were invited to switch to VPZ treatment. After an 8-week-course of once-daily VPZ (20 mg), MII-pH monitoring was repeated to compare gastric acid exposure times (GAETs), EAETs, and other reflux parameters relative to the baseline values. Before each MII-pH study, reflux symptom severities were scored using the Gastrointestinal Symptom Rating Scale; erosive esophagitis and fasting plasma gastrin levels were also assessed.

Results: From among the 124 patients undergoing MII-pH monitoring during the 4-year study period, 75 had completed at least eight weeks of appropriate PPI therapy, including 21 with documented abnormal EAEs. A total of 13 patients (median age, 69 years; females, 64%) were monitored at baseline (following at least 8 weeks of appropriate PPI therapy) and after VPZ therapy. The median GAET associated with VPZ treatment (23.8%) was less than that for PPI treatment (41.1%; $p = 0.01$), including both daytime and night-time measurements. VPZ therapy resulted in better median EAET values (4.5%) than did PPI therapy (10.6%) during the 24-h monitoring period ($p = 0.055$). EAE normalization was achieved in 46% of VPZ-treated patients and was associated with complete gastric acid suppression ($p = 0.005$). After switching to VPZ, reflux symptoms ($p < 0.01$) and erosive esophagitis ($p = 0.01$) improved.

Conclusions: In patients with PPI-refractory GERD, VPZ provides more potent gastric acid suppression, more effective esophageal acid exposure control, enhanced symptom improvement, and better esophagitis healing than PPIs.

2. Introduction

Acid suppression using proton pump inhibitors (PPIs) is the first-line approach for treating gastroesophageal reflux disease (GERD). However, approximately one-third of patients with GERD fail to respond symptomatically, either partially or completely, to PPI treatment and may seek further medical care [1]. The failure of PPI treatment to control reflux symptoms has become one of the most common GERD presentations in gastrointestinal clinical practice, and often poses considerable challenges to clinicians. Moreover, PPI-refractory GERD represents an expensive clinical problem due to the need for repeated utilization of healthcare resources, such as clinic visits, diagnostic tests, and prescription medications [2].

PPI-refractory GERD may be caused by either non-reflux- or reflux-related factors. After non-GERD etiologies have been ruled out, reflux monitoring using multichannel intraluminal impedance-pH (MII-pH) monitoring is currently used to evaluate the pathophysiology of PPI failure and to guide further treatment strategies [3, 4]. Such monitoring is useful to quantify reflux events and assess the relationship between reflux episodes and patient symptoms. It also enables further characterization of refractory patients as the studies may reveal PPI failure with ongoing acid reflux;

adequate acid control, but ongoing symptomatic non-acid reflux; or no abnormal levels of reflux. Approximately 16% of patients who experience persistent GERD symptoms, despite PPI therapy, have ongoing abnormal acid exposure [4]. For these patients, acid-suppressive drugs that are stronger or longer acting than the currently available pharmaceuticals may provide improved symptom relief.

Potassium-competitive acid blockers (P-CABs) belong to a new class of gastric acid suppressive agents that act by inhibiting gastric H^+, K^+-adenosine triphosphatase in a K^+-competitive and reversible manner. Vonoprazan (VPZ) is a novel P-CAB, discovered and developed by Takeda Pharmaceuticals (Osaka, Japan), which was launched in February 2015 for the treatment of acid-related disorders and as an adjunctive therapy in *Helicobacter pylori* eradication. The safety, tolerability, pharmacokinetics, and pharmacodynamics of single- and repeat-doses of VPZ have been evaluated in Asians and Caucasians [6 ,7]. The acid-inhibitory effects of 20-mg VPZ, compared with those of conventional PPIs, were evaluated in a randomized cross-over study, and showed more rapid, potent, and sustained suppression of gastric acid secretions in healthy volunteers [8]. These effects appear to be related to VPZ's greater

accumulation in, and subsequent slower clearance from, gastric tissue [9]. Moreover, VPZ therapy was reported to be non-inferior to lansoprazole for the healing of erosive esophagitis, at 8 weeks; patients also remained in remission for over 52 weeks [10]. Recent studies have shown the effectiveness of VPZ for treating cases of erosive esophagitis that were endoscopically shown to demonstrate incomplete healing when treated with PPIs [11-13]. Nonetheless, the clinical utility of VPZ in patients with PPI-refractory acid reflux, documented using MII-pH monitoring, remains unclear. This study aimed to evaluate the efficacy of VPZ in patients with refractory GERD who continue to exhibit pathological esophageal acid exposure (EAE), despite conventional PPI treatment.

3.0 Methods

3.1 *Patients*

Patients were retrospectively selected from among those with persistent symptoms, despite anti-secretory therapy, who had been referred for ambulatory MII-pH monitoring between November 2012 and September 2016. Patients were selected if

120 they had (1) persistent GERD symptoms despite at least eight weeks of appropriate PPI
121 therapy approved in Japan (either a heartburn or regurgitation sub-score ≥3 in the
122 Gastrointestinal Symptom Rating Scale [GSRS]), (2) pathological esophageal acid
123 exposure (esophageal pH < 4 for ≥4% of the time), documented using MII-pH, while
124 undergoing PPI therapy, and (3) been re-evaluated, using MII-pH monitoring, after
125 eight weeks of VPZ (20 mg) therapy. Patients with achalasia, eosinophilic esophagitis,
126 esophageal strictures, or past histories of upper abdominal surgeries were excluded.
127 Appropriate PPI therapy, in this study, constituted once-daily omeprazole (20 mg),
128 lansoprazole (30 mg), rabeprazole (10 mg or 20 mg), or esomeprazole (20 mg),
129 according to studies that have assessed the relative potency of PPIs based on erosive
130 esophagitis healing and gastric acid suppression [14-16].
131 The study protocol was approved by the Ethics Committee of the National Center for
132 Global Health and Medicine (Tokyo, Japan). The study was conducted in accordance
133 with the principles of the Declaration of Helsinki and written informed consent was
134 obtained from all individuals before performing MII-pH monitoring.
135
136 **3.2** ***MII-pH Monitoring***

After an overnight fast, an MII-pH catheter was inserted transnasally and placed to allow monitoring of intraluminal impedance changes at 3, 5, 7, 9, 15, and 17 cm above the manometrically located proximal border of the lower esophageal sphincter (LES). In addition, pH was monitored 5 cm above and 10 cm below the proximal border of the LES. The catheter was connected to a portable data logger (Sleuth, Sandhill Scientific, Highlands Ranch, CO, USA). During data acquisition, patients consumed standardized meals (total calories, 1800 kcal; carbohydrates, 285 g; protein, 70 g; fat, 45 g) and recorded symptoms, meal times, and posture changes using event markers on the data logger. pH-impedance tracings were analyzed using a dedicated software program (BioView Analysis, Sandhill Scientific, Highlands Ranch, CO, USA), coupled with a 2-min visual analysis to ensure accurate automated capturing of reflux events.

Esophageal acid exposure was calculated as the percent of time that the esophageal pH was <4 (esophageal acid exposure time, EAET), and gastric acidity was expressed as the percent of time that the gastric pH was <4 (gastric acid exposure time, GAET). An EAET of ≥4.0% was considered abnormal. Additionally, complete gastric acid suppression was defined as a GAET of <4%, which is the level of acid suppression

153 required to adequately control EAET and effectively promote healing of erosive
154 esophagitis [17].
155 The number of total reflux episodes (liquid and mixed reflux detected in at least the
156 two most distal impedance sites) was computed. The bolus clearance time is the
157 percentage of time that the refluxate was in contact with the distal esophageal
158 impedance electrodes, located 5 cm above the LES.
159 We defined the nocturnal period as the period between 22:00 h and 06:00 h, regardless
160 of whether the patient was recumbent; the remaining time was designated as the
161 daytime period. Nocturnal gastric acid breakthrough was defined as a drop in the
162 intragastric pH to <4 for at least 1 h during the nocturnal period.
163 When MII-pH testing was performed while patients were on-therapy, they continued to
164 take their medications for at least eight weeks. PPIs were taken before breakfast and,
165 in the case of split-dosing, before dinner. For patients with pathological EAETs during
166 the initial appropriate PPI therapy, VPZ (20 mg) was administered after breakfast for
167 eight weeks; patients were invited to be re-evaluated, using MII-pH testing, while
168 taking VPZ. To ensure medication compliance during the pH study, patients were asked
169 if they had taken their medication on each of the previous seven days. If not, the pH

study was rescheduled for another time. No other antacids or anti-secretory drugs were given during the MII-pH study period.

3.3 *Procedures*

All patients were tested for the presence of anti-*H. pylori* IgG antibodies and the presence of a cytochrome P450 (CYP) 2C19 genotype. Fasting serum gastrin levels were checked on the MII-pH testing days. Patient symptoms were assessed using the GSRS, which is a disease-specific instrument composed of 15 items, in 5 symptom clusters (reflux, abdominal pain, ingestion, diarrhea, and constipation) [18]. The GSRS has a 7-point, graded, Likert-type scale, where 1 represents the absence of troublesome symptoms and 7 represents the presence of very troublesome symptoms. The reliability and validity of the GSRS are well-documented, and normal values for a general population are available [19].

Esophagogastroduodenoscopy was performed, using a high-definition endoscope, to confirm the presence or absence of erosive esophagitis, large (>3 cm) hiatal hernias [20], and columnar-lined esophagus (>1 cm) [21].

3.4 *Data analysis*

Continuous data are expressed as means ± standard deviations or medians (range or interquartile range, IQR), as appropriate. Categorical data are expressed as numbers (percentages) of patients with a specified condition or clinical variable. Comparisons between two groups were performed using the Mann-Whitney or Wilcoxon signed-rank tests. Categorical data were compared using the Fisher's exact or Chi-squared tests, as appropriate. Statistical analyses were performed using SPSS 24.0.0 software for Macintosh (IBM, Armonk, NY, USA). All tests were two-tailed and a p-value ≤ 0.05 was considered statistically significant in all analysis.

3.5 *Sample size calculation*

Based on a previous study assessing the gastric acid suppressive effects of esomeprazole and VPZ in 10 healthy adults, the Day 7 gastric pH was >4 for 61.2 ± 17.1% of the time in the esomeprazole group and for 85.8 ± 14.7% of the time in the VPZ group [22]. Using a two-tailed alpha of 0.05 and a 95% power, the required sample size was estimated to be 8 patients.

204

205 **4. Results**

206 **4.1** ***Demographics and clinical characteristics***

207 Figure 1 shows the patient selection process. Of the 124 patients who underwent MII-
208 pH monitoring during the 4-year study period, 75 had taken at least eight weeks of
209 appropriate PPI therapy. Of those, 21 had documented, abnormal EAEs and eight
210 declined enrollment. Thus, a total of 13 patients finally agreed to switch to VPZ and to
211 be re-evaluated with MII-pH monitoring after eight weeks of the modified therapy. The
212 median lag time between the two MII-pH studies (performed while each patient was
213 undergoing PPI therapy and after VPZ therapy) was 277 days (IQR, 116–844); none of
214 the patients underwent anti-reflux surgery and all were clinically managed using
215 additional medications, such as antacids or alginates. The baseline characteristics of
216 these patients are shown in Table 1. Most of the patients (median age, 69 years) were
217 non-obese females. Five patients (38%) had scleroderma, and all had undergone at least
218 eight weeks of appropriate PPI therapy. None of the patients had evidence of current
219 *H. pylori* infections and their medical records did not suggest a history of eradication
220 therapy. Further, their CYP 2C19 genotypes were identified as being homozygous

221 extensive metabolizers (3, 23%), heterozygous extensive metabolizers (8, 62%), or
222 poor metabolizers (2, 15%).
223 Esophagogastroduodenoscopy during PPI therapy revealed erosive esophagitis in eight
224 patients (62%), four (31%) had large hiatal hernias, and four (31%) had short-segment
225 Barrett's esophagus.
226 Symptom severity, using the GSRS questionnaire while on appropriate PPI therapy,
227 included a median heartburn sub-score of 4.0 and a median regurgitation sub-score of
228 3.0.
229
230 **4.2** ***Gastric acid suppression*** (Table 2) (Fig. 2)
231 During the 24-h monitoring period, the median GAET was significantly lower when
232 patients were being treated with VPZ than when they were treated with PPIs ($p = 0.01$),
233 which was reflected in both the daytime ($p = 0.046$) and night-time ($p = 0.01$)
234 observations. Similarly, the median gastric pH was significantly higher during VPZ
235 treatment, during all monitored periods, than during PPI treatment.

Moreover, complete gastric acid suppression was achieved in 38% of patients on VPZ, compared with 0% of patients on PPIs. Nocturnal gastric acid breakthrough was less common in patients treated with VPZ than when treated with PPIs (85% vs. 54%).

4.3 *EAE and reflux episodes*

The median EAET was lower for patients treated with VPZ than for patients treated with PPIs during the 24-h monitoring period ($p = 0.055$), and EAET normalization was achieved in 46% of patients treated with VPZ (Table 2). In addition, EAET normalization was observed in all patients with complete gastric acid suppression, but in only 13% of those without ($p = 0.005$) (Fig. 3). Although the median total numbers of reflux and non-acid reflux episodes were similar between PPI and VPZ treatments ($p = 0.94$), the median number of acid reflux episodes was significantly lower during VPZ treatment than during PPI treatment ($p = 0.03$). Similarly, the bolus clearance times were similar when the patients were treated with either PPI or VPZ ($p = 0.89$) (Table 2).

4.4 *Symptoms, endoscopic findings, and fasting serum gastrin levels* (Table 3)

253 Reflux symptoms, such as heartburn and regurgitation, improved markedly after the
254 patients switched to VPZ from PPI treatment (heartburn, $p = 0.003$; regurgitation, $p =$
255 0.005; reflux dimension scores, $p = 0.001$). However, the non-reflux symptoms,
256 abdominal pain, indigestion, diarrhea, and constipation, did not change between
257 treatments.
258 Endoscopically, erosive esophagitis was present in 62% of the patients treated with
259 PPIs but healed in all except one patient (8%) treated with VPZ ($p = 0.01$).
260 The levels of fasting plasma gastrin were higher during VPZ treatment than during PPI
261 treatment ($p < 0.01$).
262
263
264 **5. Discussion/Conclusion**
265 According to the current guidelines, patients with refractory GERD symptoms and who
266 have negative endoscopy evaluations should undergo ambulatory reflux monitoring to
267 explore the underlying mechanisms of their symptoms [3, 4]. When testing patients
268 currently being treated with PPIs, MII-pH monitoring is preferred over pH monitoring
269 as it enables the characterization of refractory patients into three types: those with

persistent acid reflux, persistent non-acid reflux, or no evidence of reflux. Patients with ongoing acid reflux, despite PPI treatment, require therapy escalation to control acid reflux. Recent studies have suggested that abnormal EAETs (i.e., ≥4.0%) offer value for predicting symptomatic responses to medical or surgical therapies [23, 24]. The prevalence of abnormal EAETs was reported to be 16% in patients with typical GERD symptoms being treated with PPIs [5], increasing to as high as 40–62% in patients with Barrett's esophagus and being treated with PPIs [25]. This is the first study to evaluate the efficacy of VPZ in patients with PPI-refractory GERD and abnormal EAEs. The study demonstrates that VPZ (20 mg) provides more potent gastric acid suppression than do conventional PPIs and is more effective at controlling EAE, improving reflux symptoms, and healing erosive esophagitis.

Several studies have assessed the effects of VPZ in patients with PPI-refractory GERD. For example, Hoshino et al. evaluated 24 patients with PPI-resistant reflux esophagitis and showed that 21 (87.5%) achieved endoscopic healing following VPZ (20 mg) therapy [11]. Okuyama et al. included 54 patients with PPI-refractory GERD symptoms and showed symptomatic responses to VPZ (20 mg) treatment in 28 (51.9%) [26]; co-

existing functional dyspepsia, sleep disturbances, and alcohol abstinence were associated with the patients not demonstrating responsiveness to VPZ treatment. In addition, two studies assessed the effects of VPZ using MII-pH monitoring. Iwakiri et al. evaluated the acid-inhibitory effects of 20- (n = 9) and 40-mg (n = 10) VPZ doses in patients with PPI-resistant erosive esophagitis [12]. After 2 weeks of therapy, both groups showed significant increases in the percentages (mean) of time that the gastric pH was ≥4 (20 mg: pre-VPZ, 73.2%; post-VPZ, 96.5%; 40 mg: pre-VPZ, 70.0%; post-VPZ, 100.0%); healing of esophagitis after eight weeks of therapy was seen in 8 of 12 patients (66.7%) who completed the study and were diagnosed with esophagitis prior to therapy. Yamashita et al. assessed the effect of four weeks of VPZ (20 mg) treatment in eight patients with erosive esophagitis refractory to PPI treatment [13]. A significant increase was observed in the median gastric pH >4 holding time ratio (HTR) from 26.5% to 78.0% ($p = 0.029$) and a reduction of the median esophageal pH <4 HTR was also observed, from 7.6% to 1.1% ($p = 0.44$); 87.5% of the patients achieved esophagitis healing. These results, combined with those from the present study, may indicate a potential role for VPZ in the treatment of PPI-refractory GERD, especially in patients with persistent acid reflux documented by impedance-pH monitoring or in

304 those with esophagogastroduodenoscopy-documented erosive esophagitis during PPI
305 therapy.
306
307 Although VPZ was reported to produce more rapid healing than PPIs, Ashida et al.
308 reported that the proportions of patients demonstrating erosive esophagitis healing
309 following VPZ (20 mg) treatment increased over time: 90.7% (week 2), 96.6% (week
310 4) and 99.0% (week 8) for all patients, and 88.0% (week 2), 96.0% (week 4) and 98.7%
311 (week 8) for patients with severe reflux esophagitis [10]. Since we studied PPI-
312 refractory patients, we assumed that there would be a larger difference between
313 outcomes at weeks 4 and 8; hence, we performed EGD and MII-pH monitoring after
314 eight weeks of VPZ therapy. As mentioned previously, post-VPZ endoscopic healing
315 rates in PPI-resistant erosive esophagitis patients vary between studies; e.g., 87.5% (n
316 = 24, week 4) in a study by Hoshino [11], 66.7% (n = 12, week 8) in a study by Iwakiri
317 [12], and 87.5% (n = 8, week 4) in one by Yamashita [13]. In our study, one patient did
318 not achieve endoscopic esophagitis healing, demonstrating scleroderma and a large
319 hiatal hernia (EAET, 27.3%), despite eight weeks of VPZ treatment.
320

Scleroderma patients were previously shown to have greater acid exposure than controls, despite high-dose-PPI therapy, in a case-controlled, retrospective study that included 38 scleroderma and 38 non-scleroderma (control) patients matched for PPI formulation and dose, hiatal hernia size, age, and sex. The study demonstrated that 61% of the scleroderma patients and 18% of the control patients had total EAETs ≥4.5% [27]. In the present study, we failed to find any demographic predictors, including the presence of scleroderma (data not shown), of EAET normalization by VPZ therapy. However, this might be due to the small sample size; further studies with larger patient groups are warranted to better define the predictors of improved outcomes associated with VPZ therapy.

VPZ overcomes many weaknesses of traditional PPI therapies (short half-lives, acid lability requiring acid protection, inhibition of only activated proton pumps, requiring 3–5 doses before achieving the full effect, and clinical variability related to CYP 2C19 polymorphisms), resulting in a drug that is more potent and longer acting than conventional PPIs [27]. The relative PPI potency, defined as omeprazole equivalents, of VPZ has been determined in Western populations, based on intragastric pH >4 HTR.

In one study that included 48 healthy individuals from the UK, the mean intragastric pH >4 HTRs after 7 days of 10-, 20-, 30-, and 40-mg doses of VPZ were reported to be 60.2%, 85.2%, 90.1%, and 93.2%, respectively [7]. Extrapolating those results to the pH >4 HTR for PPIs suggests that 10 mg of VPZ, once daily, is approximately equivalent to 60 mg of omeprazole and that 20 mg of VPZ is approximately equivalent to 60 mg of omeprazole, twice daily, or 40 mg of esomeprazole, twice daily [15].

The safety profile of VPZ is a matter of concern because VPZ exerts more profound gastric acid inhibition than PPIs. However, no serious, drug-related, treatment emergent adverse events were identified during clinical development and the clinical safety profile of VPZ has been reported to be comparable to those of other PPIs [8, 10]. In the present study, fasting plasma gastrin levels were elevated to >4-fold of the upper limit of normal. A 52-week esophageal healing maintenance study showed progressive increases in serum gastrin levels, rising from 318 ± 336 pg/mL after eight weeks of treatment to 778 ± 679 pg/mL after 52 weeks of VPZ (20 mg) treatment. Treatment with 10-mg doses resulted in a rise from 291 ± 220 pg/mL to 514 ± 436 pg/mL, at similar time points. At both treatment doses, there were no significant effects on gastric

355 neuroendocrine cells at 24 or 52 weeks of therapy, nor were changes in pepsinogen
356 levels observed. A long-term VPZ safety trial is currently underway to
357 histopathologically evaluate the gastric mucosa for evidence of neoplastic alterations
358 of the gastric mucosal epithelial cells, as well as other adverse events [28].
359
360 The limitations of this study include its small sample size, lack of a control group, and
361 the retrospective identification of patients; the data were collected prospectively. As
362 described previously [4], only a small proportion of patients experiencing persistent
363 GERD symptoms, despite PPI therapy, have ongoing abnormal acid exposure. Thus,
364 one of the strengths of this study was the actual measurement of gastric acid
365 suppression, by MII-pH monitoring, over 24-hour period both before and after VPZ
366 therapy in this number of patients. The study also allowed precise identification of
367 patients with ongoing reflux and requiring more aggressive acid suppression from
368 among all patients with disease refractory to PPI therapy. The use of a standardized
369 questionnaire to evaluate symptoms was also a strength of the study. Further, despite
370 the study's limitations, our findings support the clinical utility of VPZ as a novel gastric
371 acid suppressive medication in selected patients with PPI-refractory GERD.

In conclusion, in patients with PPI-refractory GERD and continued pathological esophageal acid exposure, VPZ (20 mg) provides more potent gastric acid suppression and is more effective than PPIs for controlling EAE, improving symptoms, and healing esophagitis.

6. Statements

6.1 Acknowledgements

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6.2 Statement of Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki and written informed consent was obtained from all individuals before performing MII-pH monitoring. The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (Tokyo, Japan).

6.3 Disclosure Statement

Junichi Akiyama, Naomi Uemura, Hiroko Hosaka, Shiko Kuribayashi, and Motoyasu Kusano have served as speakers for Takeda Pharmaceutical Company and Otsuka Pharmaceutical Company. Motoyasu Kusano has received research funding from Takeda Pharmaceutical Company.

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6.5 Author Contributions

Junichi Akiyama, Shiori Moriyasu, Yuya Hisada, Hidetaka Okubo, Kazuhiro Watanabe, Koh Imbe, Naoyoshi Nagata, Yasushi Kojima, Chizu Yokoi, and Naomi Uemura collected data. Junichi Akiyama, Hiroko Hosaka, Shiko Kuribayashi, Yasuyuki Shimoyama, Osamu Kawamura, Masanobu Yamada, and Motoyasu Kusano analyzed the data. Junichi Akiyama, Hiroko Hosaka, Shiko Kuribayashi, and Motoyasu Kusano designed the research study and wrote the paper.

All authors reviewed and approved the final version of the article, including the authorship list.

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Figure Legends

Fig. 1. Study flowchart. Of the 124 patients undergoing multichannel intraluminal impedance-pH (MII-pH) monitoring during the almost 4-year study period, 75 had undergone at least 8 weeks of appropriate proton pump inhibitor (PPI) therapy. Of those, abnormal esophageal acid exposure was documented in 21 patients; 8 patients declined enrollment. Thus, a total of 13 patients agreed to switch to vonoprazan therapy and to be re-evaluated after 8 weeks of therapy.

Fig. 2. Representative tracings of the multichannel intraluminal impedance-pH (MII-pH) monitoring study (a) upon conclusion of 20-mg rabeprazole therapy (baseline) (EAET = 19.7%, GAET = 36.5%) and (b) after 8 weeks of 20-mg vonoprazan therapy, showing complete gastric acid suppression (EAET = 0%, GAET = 0%)

EAET, Esophageal acid exposure time; GAET, gastric acid exposure time

Fig. 3. Association between gastric acid suppression and esophageal acid exposure during vonoprazan therapy. Normalization of esophageal acid exposure time was

527 achieved in 46% of patients treated with vonoprazan, and it was generally associated

528 with gastric acid suppression sufficient for esophagitis healing (GAET <4%).

529 PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; EAE, esophageal

530 acid exposure; GAET, gastric acid exposure time

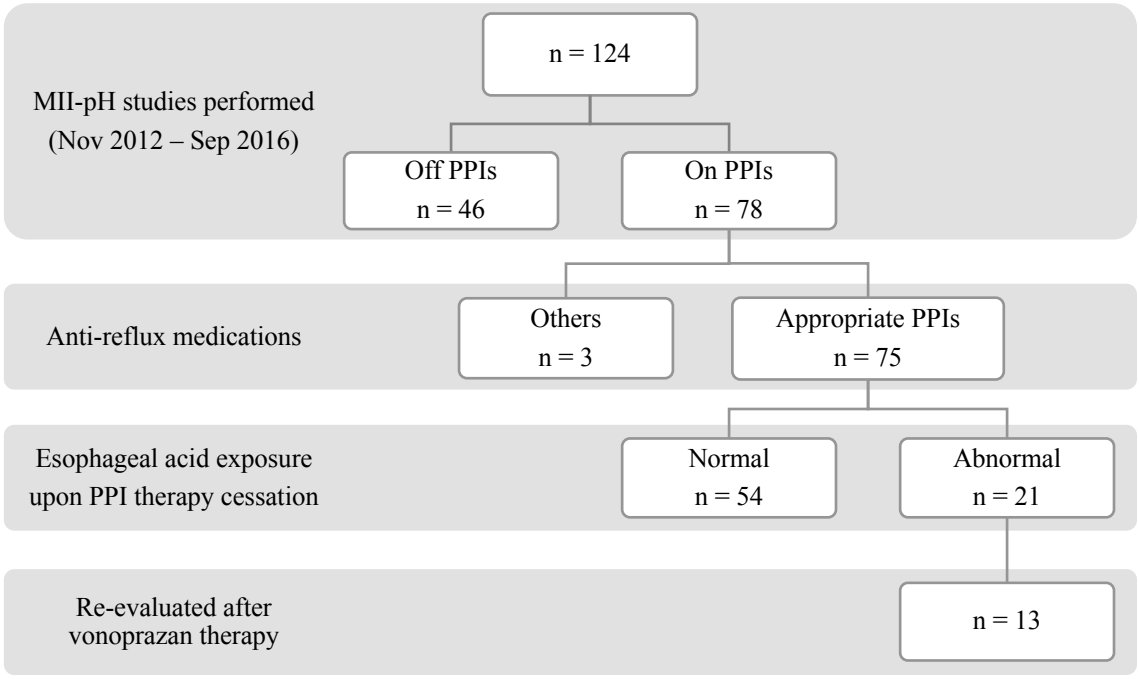
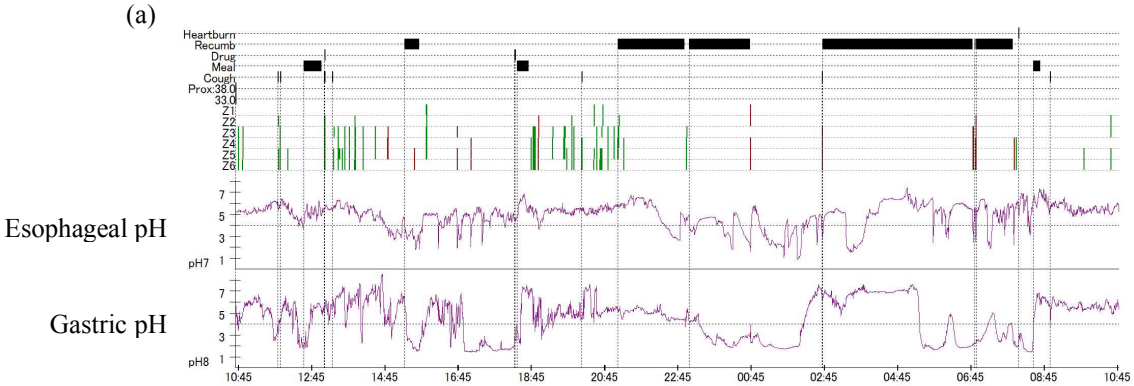

MII-pH studies performed
(Nov 2012 – Sep 2016)
n = 124
Off PPIs
n = 46
On PPIs
n = 78
Anti-reflux medications
Others
n = 3
Appropriate PPIs
n = 75
Esophageal acid exposure
upon PPI therapy cessation
Normal
n = 54
Abnormal
n = 21
Re-evaluated after
vonoprazan therapy
n = 13

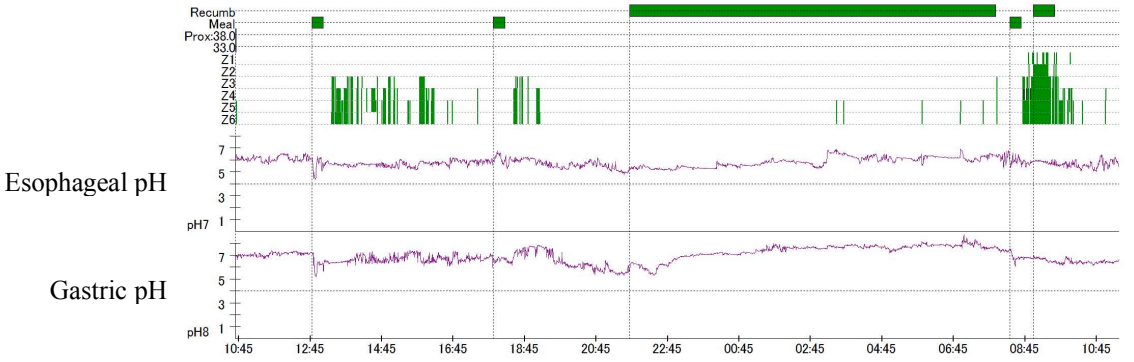
Figure 1

(a)



Time (h)

(b)



Time (h)

Figure 2

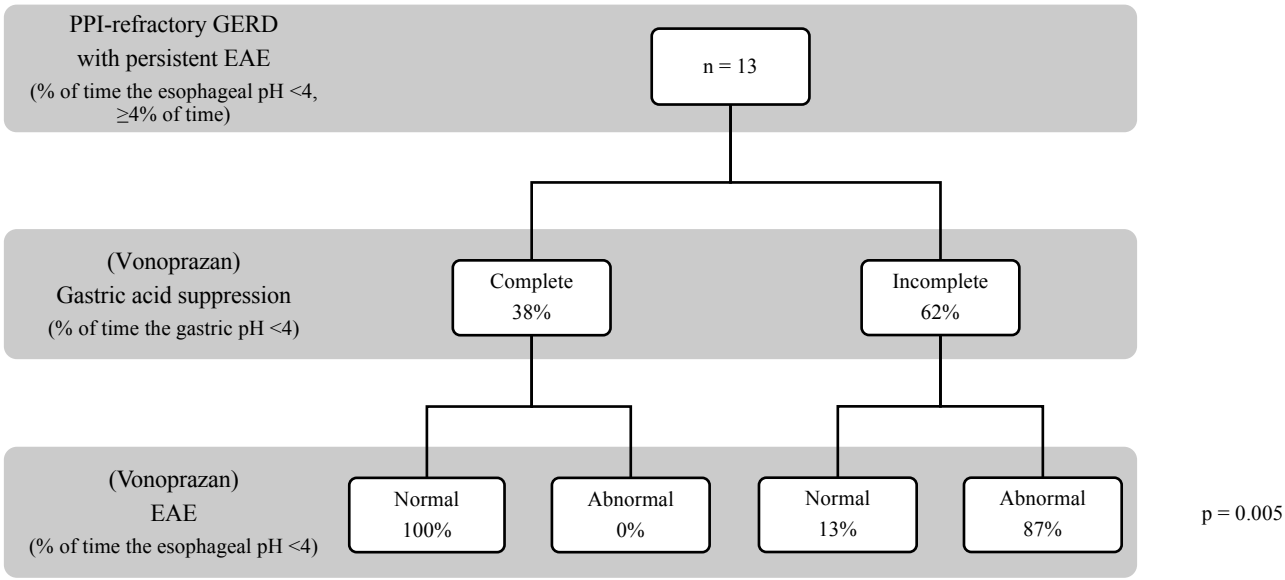

PPI-refractory GERD
with persistent EAE
(% of time the esophageal pH <4,
≥4% of time)
n = 13
(Vonoprazan)
Gastric acid suppression
(% of time the gastric pH <4)
Complete
38%
Incomplete
62%
(Vonoprazan)
EAE
(% of time the esophageal pH <4)
Normal
100%
Abnormal
0%
Normal
13%
Abnormal
87%
p = 0.005

Fig. 3

Table 1. Baseline characteristics of patients treated with vonoprazan for proton pump inhibitor (PPI)-refractory gastroesophageal reflux disease

Variables	**n = 13**
Age, years, median (range)	69.0 (47–82)
Sex (Female), n (%)	9 (64%)
Body mass index, median (range)	20.3 (16.4–24.8)
Comorbidity: scleroderma, n (%)	5 (38%)
Proton pump inhibitors, n (%)	
Omeprazole, 20 mg	2 (15%)
Lansoprazole, 30 mg	4 (31%)
Esomeprazole, 20 mg	2 (15%)
Rabeprazole, 20 mg	5 (38%) #
***Helicobacter pylori* infection**, n (%)	0 (0%)
Cytochrome P450 2C19 genotype, n (%)	
Homozygous extensive metabolizer	3 (23%)
Heterozygous extensive metabolizer	8 (62%)
Poor metabolizer	2 (15%)
Esophagogastroduodenoscopy findings (on PPIs)	
Erosive esophagitis, n (%)	8 (62%)
Los Angeles classification (none/A/B/C/D), n	5/4/2/2/0
Hiatal hernia (>3 cm), n (%)	4 (31%)
Short-segment Barrett's esophagus (>1 cm), n (%)	4 (31%)
Symptom severity (GSRS reflux dimension) (on PPIs), median (IQR)	
Heartburn	4.0 (2.5–4.5)
Regurgitation	3.0 (2.0–5.0)

GSRS, Gastrointestinal Symptom Rating Scale; IQR, interquartile range

single-dose (n = 2), split-dose (n = 3)

Table 2. Comparisons of multichannel intraluminal impedance-pH monitoring findings between proton pump inhibitor (PPI) and vonoprazan therapies.

	PPIs (n = 13)	Vonoprazan (n = 13)	p value
Gastric acidity			
All day			
GAET (% time with gastric pH <4)	41.1 (33.9–59.6)	23.8 (0.7–35.1)	**0.01**
Median gastric pH	4.4 (3.6–4.9)	5.1 (4.8–6.4)	**0.04**
Complete gastric acid suppression (GAET <4%), n (%)	0 (0%)	5 (38%)	
Daytime			
GAET (% time with gastric pH <4)	35.9 (29.3–60.7)	16.1 (0.9–29.5)	**0.046**
Median gastric pH	4.6 (3.7–5.2)	5.6 (5.2–6.2)	**0.056**
Night-time			
GAET (% time with gastric pH <4)	63.6 (43.7–79.9)	33.5 (0.0–58.0)	**0.01**
Median gastric pH	3.2 (2.6–4.4)	5.2 (3.7–6.7)	**0.02**
Nocturnal gastric acid breakthrough, n (%)	11 (85%)	7 (54%)	0.73
Esophageal acid exposure			
All day			
EAET (% time with esophageal pH <4)	10.6 (6.5–18.7)	4.5 (0.2–8.8)	**0.055**
Median esophageal pH	5.5 (5.2–5.6)	5.7 (5.3–5.8)	0.35
Normal EAET (EAET <4%), n (%)	0 (0%)	6 (46%)	
Daytime			
EAET (% time with esophageal pH <4)	9.5 (6.8–10.8)	0.9 (0.0–6.7)	0.15
Median esophageal pH	5.6 (5.2–5.8)	5.6 (5.2–5.8)	0.81
Night-time			
EAET (% time with esophageal pH <4)	12.7 (6.0–29.1)	0.0 (0.0–14.0)	0.31
Median esophageal pH	5.1 (4.7–5.4)	5.4 (4.9–5.9)	0.31
Number of reflux episodes			
Total	57 (20–69)	50 (14–62)	0.27
Acid	11 (4–33)	1 (0–11)	**0.03**
Non-acid	33 (13–42)	23 (10–53)	0.94
Bolus clearance time, %	5.7 (2.5–7.9)	2.5 (0.4–10.3)	0.89

Values are expressed as medians (interquartile range) or n (%)

PPI, proton pump inhibitor; EAET, esophageal acid exposure time; GAET, gastric acid exposure time

Table 3. Comparisons of symptom intensity, erosive esophagitis, and fasting serum gastrin level between proton pump inhibitor (PPI) and vonoprazan therapies

	PPIs (n = 13)	Vonoprazan (n = 13)	p value
Symptom intensity (GSRS sub-dimension scores), median (IQR)			
Reflux	3.0 (2.3–5.0)	1.5 (1.0–2.5)	**0.001**
Heartburn	4.0 (2.5–4.5)	2.0 (1.5–2.5)	**0.003**
Regurgitation	3.0 (2.0–5.0)	1.0 (1.0–2.5)	**0.003**
Abdominal pain	1.7 (1.2–2.8)	1.3 (1.0–2.5)	0.194
Indigestion	1.8 (1.4–3.6)	2.0 (1.4–2.4)	0.246
Diarrhea	1.3 (1.2–2.0)	1.7 (1.0–2.8)	0.919
Constipation	2.3 (1.2–3.5)	2.0 (1.2–3.7)	0.581
Erosive esophagitis (on antisecretory therapy)			
Los Angeles classification (None/A/B/C/D), n	5/4/2/2/0	12/1/0/0/0	**0.01**
Fasting serum gastrin, pg/mL (median (IQR))	468 (390–692)	851 (726–1830)	**0.007**

GSRS, Gastrointestinal Symptom Rating Scale; IQR, interquartile range