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Vonoprazan Therapy is as Effective for Functional Dyspepsia without Heartburn as Acotiamide Therapy

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ABSTRACT

Background & Aims: Acid suppression improves dyspepsia symptoms but the efficacy of vonoprazan for functional dyspepsia remains unclear. The aim of this study is to evaluate the effectiveness of vonoprazan therapy for functional dyspepsia without heartburn.

Methods: Patients receiving vonoprazan 10 mg once daily or acotiamide 100 mg three times daily for more than one month were included and retrospectively reviewed. Functional dyspepsia was diagnosed based on the ROME IV criteria. Patients with heartburn were excluded. Eighty-five patients were divided into vonoprazan (n=48) and acotiamide (n=37) groups.

Results: There were no significant differences at baseline between the vonoprazan and acotiamide groups. The functional dyspepsia score significantly improved in both groups ($p<0.001$). The degree of score reduction (55% vs 59%, $p=0.559$) and the resolution rates (21% vs 30%, $p=0.345$) were similar. Epigastric pain and postprandial distress scores were significantly improved in both groups, and the degree of improvement of each score was similar. Constipation and diarrhea scores were significantly improved in both groups, and the degree of improvement similar.

Conclusion: These preliminary results suggest that vonoprazan is effective for the treatment of functional dyspepsia without heartburn in the short-term, with results similar to acotiamide therapy.

Key words: potassium-competitive acid blocker – acotiamide – gastritis - functional dyspepsia – *Helicobacter pylori* – gastroesophageal reflux disease – proton pump inhibitor.

Abbreviations: ACO: acotiamide; GI: gastrointestinal; *H. pylori: Helicobactor pylori*; PPI: proton pump inhibitor; RCT: randomized-controlled trial; VPZ: vonoprazan.

INTRODUCTION

Many people suffer from functional dyspepsia, with a prevalence of 11-17% in Japan [1]. However, the incidence of gastric cancer/ulcer is decreasing due to the widespread use of *Helicobactor pylori* (*H. pylori*) eradication therapy [2]. Despite the decreased prevalence of gastric ulcers, the most common symptoms were discomfort and/or pain in the upper gastrointestinal (GI) tract over a period of 25 years [3]. Due to the complicated pathogenesis of functional dyspepsia, definitive treatment is not yet established.

The Cochrane database of systematic reviews showed that proton pump inhibitors (PPIs) were effective for functional dyspepsia compared to placebo [4]. Symptomatic resolution was slightly better in the PPI group than the placebo group (31% vs 26%). Vonoprazan (VPZ), a novel potassium-competitive acid blocker, has been available in Japan since 2015, and has a stronger acid suppression effect compared to PPI [5]. We previously reported the effectiveness of VPZ on dyspepsia symptoms in patients with heartburn in both short and long-term studies [6, 7]. Little evidence is available for the effect of VPZ on functional dyspepsia without heartburn.

Prokinetic drugs are a standard treatment for functional dyspepsia. Acotiamide (ACO), a prokinetic drug, has been available in Japan since 2013. A randomized-controlled trial (RCT) demonstrated that ACO had led to a significant improvement compared to placebo regarding meal-related dyspepsia symptoms [8]. However, comparison of ACO therapy with VPZ for functional dyspepsia has not yet been reported.

The aim of this study was to evaluate the effectiveness of VPZ therapy on functional dyspepsia in patients without heartburn compared to ACO therapy.

METHODS

Study Population

This was a retrospective comparative study. A total of 395 patients who received VPZ or ACO therapy for functional dyspepsia from November 2014 to June 2022 were reviewed. Acotiamide was mainly used during the first half of the study period and VPZ mainly in the second half. The treatment for functional dyspepsia was changed from ACO to VPZ in 2017 because better adherence to the VPZ regimen was expected. Vonoprazan was given only once daily before or after meals, and the ACO regimen was three times daily before meals.

Inclusion criteria were: 1) diagnosis of functional dyspepsia based on the ROME IV criteria; 2) significant domain-specific score of the Izumo scale (4 points or above) in the epigastric pain or postprandial distress domains; and 3) VPZ (10 mg once daily) or ACO therapy (100 mg three times daily) administered for more than one month. Exclusion criteria were: 1) presence of heartburn (domain-specific score in heartburn of 4 points or above); 2) cessation of VPZ/ACO therapy within one month; 3) no clinic visits for more than one month; 4) VPZ/PPI/ACO therapy before starting VPZ or ACO; 5) VPZ/ PPI/ ACO added after starting VPZ/ACO; 6) dose changes of VPZ/ACO; and 7) current *H. pylori* infection. Based on these criteria, 310 patients were excluded, and 85 patients were finally included in the study cohort. These 85 patients were divided into the VPZ (n=48) and ACO (n=37) groups.

All patients underwent esophagogastroduodenoscopy before starting VPZ/ACO. The grade of gastric atrophy was classified based on the Kimura-Takemoto classification [9]. Current *H. pylori* infection status was assessed by the serum IgG level, stool antigen test and/or ^{13}C-urea breath test. *Helicobacter pylori* eradication history was confirmed by interview and/or chart review. The Institutional Review Board of the Shinozaki Medical Clinic approved this retrospective review.

Evaluation of Dyspepsia Symptoms by Izumo Scale

The Japanese Guideline for functional dyspepsia 2021 recommends a self-reporting questionnaire for initial diagnosis and judging the effectiveness of functional dyspepsia treatment [1]. The Izumo scale is a GI symptom-related quality of life assessment questionnaire that has been broadly validated [10, 11] (Fig 1). We frequently use the Izumo scale in routine clinical practice to evaluate abdominal symptoms. The Izumo

Izumo scale for abdominal symptom-related QOL

Please check ☑ the most appropriate box for each question based on your most recent one-week daily activities.		Not bothered	Not so bothered	Slightly bothered	Bothered	Strongly bothered	Intolerably bothered
Q1	Are you bothered by acid reflux?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q2	Are you bothered by heartburn centered in the anterior chest?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q3	Are you bothered by throat discomfort?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q4	Are you bothered by epigastric pain?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q5	Are you bothered by hunger epigastric pain?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q6	Are you bothered by an epigastric burning sensation?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q7	Are you bothered by early satiation?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q8	Are you bothered by post-prandial long-lasting epigastric fullness or nausea?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q9	Are you bothered by epigastric bloating?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q10	Are you bothered by a feeling of incomplete defecation?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q11	Are you bothered by constipation or hard stools?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q12	Are you bothered by stress-related constipation?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q13	Are you bothered by fecal urgency?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q14	Are you bothered by diarrhea or soft stools?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$
Q15	Are you bothered by stress-related diarrhea?	☐$_0$	☐$_1$	☐$_2$	☐$_3$	☐$_4$	☐$_5$

Fig. 1. The Izumo scale, a self-reporting questionnaire evaluating gastrointestinal symptoms (cited from Kakuta et al. [10])

scale has five domains: heartburn (Q1-3), epigastric pain (Q4-6), postprandial distress (Q7-9), constipation (Q10-12) and diarrhea (Q13-15). Each domain has three items scored from 0 to 5 on a Likert scale: 0 = not bothered, 1 = not so bothered, 2 = slightly bothered, 3 = bothered, 4 = strongly bothered and 5 = intolerably bothered [10]. Each domain-specific score was calculated from the total score of the 3 items, and therefore each domain-specific score ranges from 0 to 15. Significant symptoms were defined as 4 points or more for a domain-specific score. The functional dyspepsia score was defined as the sum of the epigastric pain and postprandial distress domains [12]. The total score was defined as the sum of the scores for all domains. Patients with a score of 4 or more in the heartburn domain were excluded from this study based on the exclusion criteria. A "resolution of symptoms" was defined as a score decreased to 1 or 0.

Statistical Analysis

Changes in scores before and after VPZ/ACO therapy were compared by the Wilcoxon rank-sum test. Differences in the degree of score reduction between the two groups were compared using the Mann-Whitney U-test. Statflex version 7.0 software (Artech Co. Ltd. Osaka, Japan) was used. Differences were considered significant when $p<0.05$.

RESULTS

The characteristics of 85 patients before starting VPZ or ACO were shown in Table I. Although all parameters were compared, there were no significant differences between the two groups at baseline. The body mass index was comparatively low, and more than half of the patients were female. Approximately one-third of patients suffered from constipation and/or diarrhea complicated by functional dyspepsia.

Functional dyspepsia scores were significantly improved in both groups ($p<0.001$) (Fig. 2a). The degree of score reduction was similar in both groups, and the difference was not significant ($p=0.559$) (Fig. 2b). The resolution rates were also similar ($p=0.345$) (Fig. 2c). Vonoprazan therapy was as effective for functional dyspepsia without heartburn as ACO therapy.

Significant epigastric pain was present in 58 patients (VPZ n=36, ACO n=22). Epigastric pain scores were significantly improved in both groups ($p<0.001$) (Fig. 3a). The degree of reduction was slightly greater in the ACO group than in the VPZ group, although the difference was not statistically significant ($p=0.225$) (Fig. 3b). The resolution rate was higher in the ACO group than the VPZ group, although the difference was not statistically significant ($p=0.208$) (Fig. 3c).

Significant postprandial distress was present in 66 patients (VPZ n=34, ACO n=32). Postprandial distress domain scores were significantly improved in both groups ($p<0.001$) (Fig. 3d). The degree of reduction was similar ($p=0.836$) (Fig. 3e). The resolution rate was also similar ($p=0.665$) (Fig. 3f). Subgroup analyses using epigastric pain or postprandial distress domains did not show significant differences between the two groups.

Thirty-four patients suffered from constipation (VPZ n=17, ACO n=17). Constipation scores were significantly improved in both groups ($p<0.02$) (Fig 4a). The degree of reduction was similar between the two groups (Fig. 4b). Twenty-nine patients had significant diarrhea symptoms (VPZ n=16, ACO n=13). Diarrhea scores were significantly improved in both groups ($p<0.02$) (Fig. 4c). The degree of reduction was similar (Fig. 4d).

The total score defined as the sum of heartburn, epigastric pain, postprandial distress, constipation and diarrhea domain-specific scores was evaluated (VPZ n=48, ACO n=37). The total scores were significantly improved in both groups by about half (Fig. 4e). The degree of reduction was similar (Fig. 4f).

Table I. Baseline characteristics of patients

	VPZ group (n=48)	ACO group (n=37)	p
Age, years, median (IQR)	46 (36-58)	48 (39-57)	0.579
Gender, male, n (%)	15 (31)	10 (27)	0.671
Body mass index, median (IQR)	20.9 (18.8-23.0)	20.7 (19.6-23.7)	0.407
Current smoker, n (%)	3 (6)	5 (13)	0.255
History of *H. pylori* eradication, n (%)	14 (29)	8 (22)	0.431
Functional dyspepsia score, baseline, median (IQR)	9.0 (7.0-12.5)	10.0 (6.0-13.0)	0.925
Significant dyspepsia symptom, n (%)			
Epigastric pain	36 (75)	22 (59)	0.127
Baseline, median (IQR)	5.5 (4.0-7.0)	7.0 (5.0-8.0)	0.084
Postprandial distress	34 (71)	32 (86)	0.085
Baseline, median (IQR)	6.0 (5.0-9.0)	6.0 (4.0-7.0)	0.620
Lower GI symptoms, n (%)			
Constipation	17 (35)	17 (46)	0.325
Baseline, median (IQR)	5.0 (5.0-7.0)	6.0 (4.0-7.3)	0.805
Diarrhea	16 (33)	13 (35)	0.862
Baseline, median (IQR)	5.5 (4.0-7.5)	7.0 (5.0-7.5)	0.361
Total score, baseline, median (IQR)	17.0 (11.0-20.5)	17.0 (12.0-24.3)	0.612
Gastric atrophy, n (%)			
Closed-type	10 (21)	3 (8)	0.106
Open-type	6 (13)	10 (27)	0.089

ACO: acotiamide; IQR: interquartile range; GI: gastrointestinal; *H. pylori: Helicobacter pylori*; VPZ: vonoprazan.

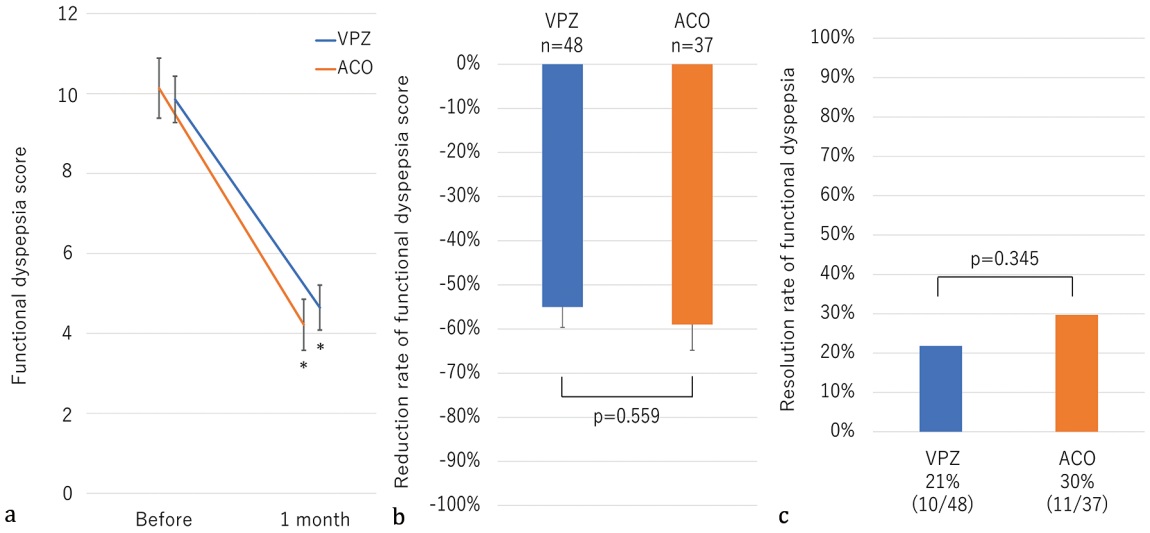

Fig. 2. Effectiveness of vonoprazan (VPZ) / acotiamide (ACO) for functional dyspepsia: a) changes in functional dyspepsia score (mean±standard error) at 1 month after starting therapy; b) reduction rate of functional dyspepsia score; c) resolution rate of functional dyspepsia. * p<0.001 compared to before starting VPZ/ACO.

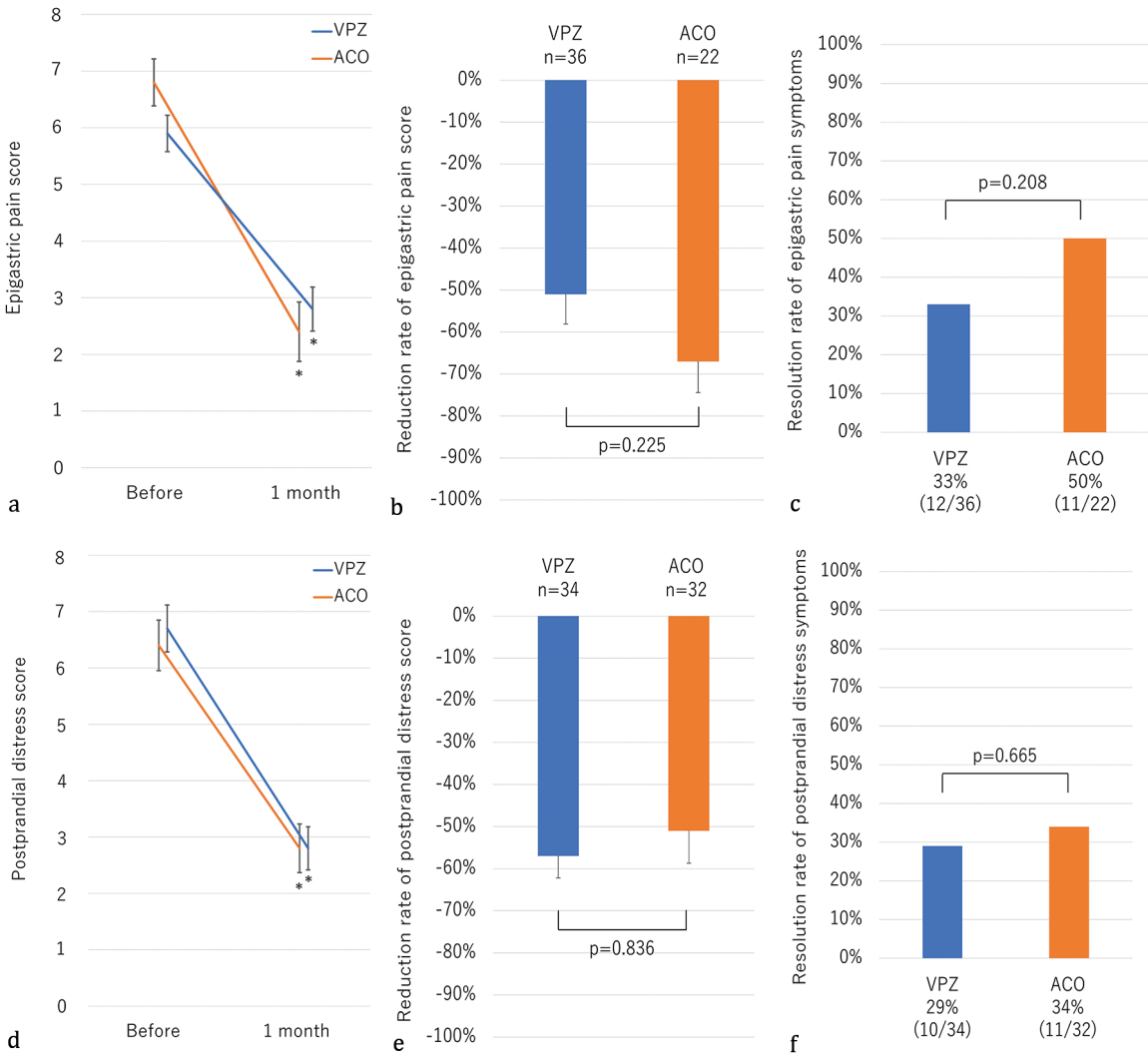

Fig. 3. Effectiveness of vonoprazan (VPZ) / acotiamide (ACO) for each domain-specific score: a) changes in epigastric pain score (mean±standard error) at 1 month after starting therapy; b) reduction rate of epigastric pain score; c) resolution rate of epigastric pain symptoms; d) changes in postprandial distress score; e) reduction rate of postprandial distress score; f) resolution rate of postprandial distress symptoms at 1 month after starting therapy. * p<0.001 compared to before starting VPZ/ACO.

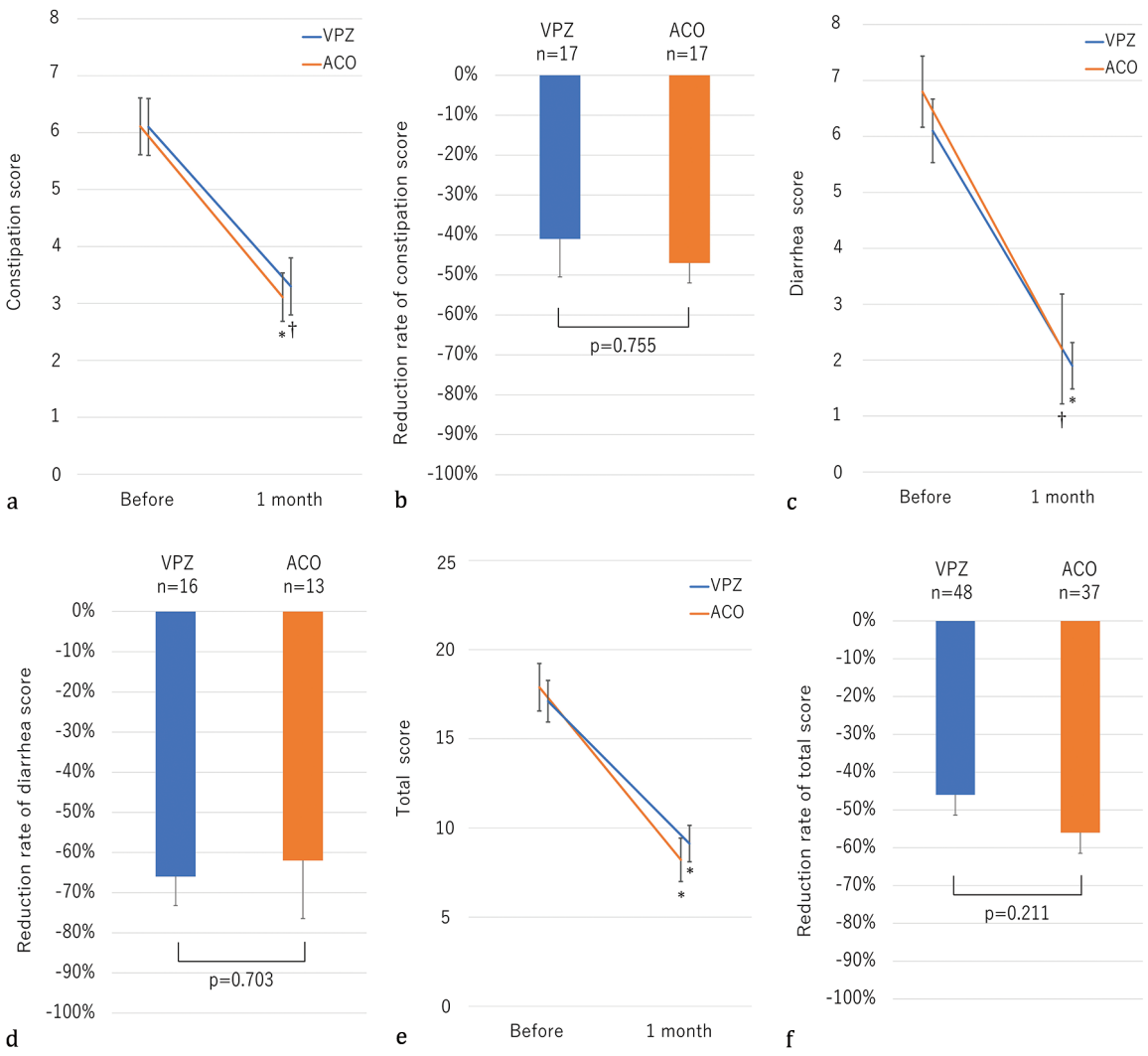

Fig. 4. Effectiveness of vonoprazan (VPZ) / acotiamide (ACO) on gastrointestinal symptoms: a) changes in constipation score (mean±standard error) at 1 month after starting therapy; b) reduction rate of constipation score; c) changes in diarrhea score at 1 month after starting therapy; d) reduction rate of diarrhea score; e) changes in total score at 1 month after starting therapy; f) reduction rate of total score. * p<0.001 compared to before starting VPZ/ACO. †p<0.02.

DISCUSSION

Treatment with both VPZ and ACO significantly improved functional dyspepsia in patients without heartburn. There were no significant differences in degrees of improvement between the two groups. Subgroup analyses of epigastric pain and postprandial distress domains did not show significant differences in improvement between the two groups. Both therapies were also effective against constipation and diarrhea. Total scores were improved by both therapies. To the best of our knowledge, this is the first study demonstrating the effectiveness of VPZ for the treatment of functional dyspepsia in patients without heartburn.

We previously reported the long-term improvement of dyspepsia symptoms by VPZ therapy in patients with heartburn [7]. Regarding functional dyspepsia with heartburn, acid suppression therapy may be the first choice. A Japanese retrospective study reported the effectiveness of 4-weeks of VPZ therapy (20 mg) on functional dyspepsia with an improvement rate of 59% [13], but patients with heartburn or current *H. pylori* infection were not excluded. A definitive strategy for functional dyspepsia without heartburn remains unclear. Although this study demonstrates that the effectiveness of VPZ is comparable to ACO, once daily treatment with VPZ may be preferable since this regimen may improve long-term compliance that is important to maintain long-term control [14]. Vonoprazan is administered both before and after a meal once daily, but ACO is only taken before meals three times daily. The use of prokinetic drugs may be welcomed by physicians who are concerned about the long-term use of acid blockers.

The major advantage of VPZ over PPI is the stable acid suppression effect regardless of the CYP2C19 genotype as well as stronger acid suppression [15]. The effect of PPI is strongly influenced by the CYP2C19 genotype. The number of acid reflux events was much less during VPZ therapy compared to PPI therapy [16]. Although there are no comparative data regarding duodenal acidity during VPZ/PPI therapy, the influx of acid into the duodenum may be much less in the VPZ than the PPI group. Since the acid suppression effect on dyspepsia

symptoms is dose dependent in *H. pylori* negative subjects according to a Japanese RCT [17], the stable acid suppression effect of VPZ regardless of CYP2C19 genotype suggests that it is more useful than PPI. An RCT evaluating the effects of VPZ on dyspepsia symptoms compared to PPI is necessary.

Dyspepsia symptoms are associated with low-grade inflammation of the duodenum caused by eosinophil infiltration due to elevated mucosal permeability [18]. Hypersensitivity to acid of gastric and duodenal mucosa is also related to the mechanism of functional dyspepsia. Acid infusion into the stomach induces various dyspepsia symptoms including a "heavy feeling" in the stomach, bloating, nausea or "feeling sick", and belching [19, 20]. Acid influx to the duodenum results in delayed gastric emptying and hypersensitivity. Duodenal acidification by transnasal endoscopy induces various dyspepsia symptoms and suppresses antral contractions [21]. Low-grade inflammation as shown by eosinophil and mast cell infiltration of the duodenum is associated with functional dyspepsia [1, 18] and acid suppression by VPZ may attenuate low-grade inflammation of the duodenum. A recent Japanese study revealed that VPZ delayed gastric emptying but increased ghrelin levels in healthy male subjects [22]. Vonoprazan surely improved dyspepsia symptoms as much as ACO did, and therefore delayed gastric emptying due to VPZ may be compensated by elevating ghrelin levels that can improve dyspepsia symptoms.

It has been clearly shown that ACO is effective for the treatment of functional dyspepsia, as confirmed by a phase III trial [8]. A systematic review revealed that PPI is more effective than prokinetic drugs for improving dyspepsia symptoms [4], but these studies did not exclude patients with heartburn. Since the influence of gastric acid is higher in patients with functional dyspepsia with heartburn than in those without heartburn, acid blockers are effective for improvement of functional dyspepsia with heartburn. Therefore, the effectiveness for functional dyspepsia with or without heartburn should be separately analyzed. The present study, which excluded patients with heartburn, demonstrates that the efficacy of VPZ is comparable to that of ACO for the treatment of dyspepsia symptoms.

We previously reported the effectiveness of VPZ and ACO on lower GI symptoms [7, 23]. A Japanese study also reported the effectiveness of VPZ on constipation in patients with PPI-resistant erosive gastroesophageal reflux disease [24]. In a long-term observational study, VPZ improved both constipation and diarrhea in symptomatic subjects, and VPZ did not aggravate these lower GI symptoms in asymptomatic subjects [7]. Acotiamide also improved not only dyspepsia symptoms but also lower GI symptoms [23]. We cannot offer a conclusive explanation why improving upper GI symptoms leads to the improvement of lower GI symptoms. But we assume that acid suppression due to VPZ improves delayed gastric emptying, impaired fundic accommodation and/or hypersensitivity disorder. Improvements in functional mechanisms and low-grade inflammation in the upper GI tract may have a salutary effect on the lower GI tract. If a patient has both upper and lower GI symptoms, upper GI symptoms should be treated first using VPZ/ACO, followed by the treatment of lower GI symptoms which can be considered after one month of treatment for upper GI tract symptoms.

This study has acknowledged strengths. Firstly, due to the easy access that patients have primary care clinics in Japan, six months of persistent dyspepsia symptoms before starting VPZ/ACO is comparatively rare. This study strictly included patients with functional dyspepsia diagnosed based on the ROME IV criteria. Secondly, patients with heartburn largely affected by gastric acid secretion were excluded, so "pure functional dyspepsia" was evaluated. Thirdly, subjects with a concurrent *H. pylori* infection were excluded, and therefore subjects with *H. pylori*-associated dyspepsia were excluded from this study. Fourthly, this is the first comparative study evaluating the effectiveness of VPZ on dyspepsia symptoms compared to prokinetics. Fifthly, lower GI symptoms were evaluated as well as upper GI symptoms. Sixthly, all patients underwent esophagogastroduodenoscopy before starting treatment. This study also has some acknowledged limitations. Firstly, this is a single-center retrospective study without a placebo group. Secondly, there is a time frame shift between the two groups. Thirdly, GI function testing was not performed. Fourthly, the number of administrations was different between two groups (once vs three times daily), and therefore placebo effects may be different.

CONCLUSIONS

Vonoprazan therapy is effective for the treatment of functional dyspepsia in patients without heartburn in the short-term, similar to ACO therapy. Lower GI symptoms also improved. An RCT is necessary to confirm the preliminary results of this retrospective comparative study.

Conflicts of interest: S.S. H.O. and Y.M. has received honoraria from Takeda and Otsuka Pharmaceuticals. H.Y. has received honoraria from Takeda Pharmaceutical. All other authors declare no conflicts of interest regarding this study.

Authors' contributions: S.S., H.O. conceived and designed the study, collected and analyzed the data, drafted the manuscript. H.Y., Y.M., H.S.: participated in the conception and design of the study and collected the data. T.Y.: participated in the conception and design of the study, analyzed, and interpreted the data analysis and wrote the manuscript. A.L. wrote the manuscript, analyzed and interpreted the data. All the authors contributed to revisions and approved the final version of the manuscript.

REFERENCES

1. Miwa H, Nagahara A, Asakawa A, et al. Evidence-based clinical practice guidelines for functional dyspepsia 2021. J Gastroenterol 2022;57:47-61. doi:10.1007/s00535-021-01843-7
2. Tsuda M, Asaka M, Kato M, et al. Effect on Helicobacter pylori eradication therapy against gastric cancer in Japan. Helicobacter 2017;22:e12415. doi:10.1111/hel.12415
3. Manabe N, Haruma K, Kamada T, et al. Changes of upper gastrointestinal symptoms and endoscopic findings in Japan over 25 years. Intern Med 2011;50:1357-1363. doi:10.2169/internalmedicine.50.4731
4. Pinto-Sanchez MI, Yuan Y, Hassan A, Bercik P, Moayyedi P. Proton pump inhibitors for functional dyspepsia. Cochrane Database Syst Rev 2017;11:CD011194. doi:10.1002/14651858.CD011194.pub3

5. Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects--a randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42:719-730. doi:10.1111/apt.13325
6. Shinozaki S, Osawa H, Hayashi Y, et al. Vonoprazan treatment improves gastrointestinal symptoms in patients with gastroesophageal reflux disease. Kaohsiung J Med Sci 2017;33:616-622. doi:10.1016/j.kjms.2017.07.004
7. Shinozaki S, Osawa H, Kobayashi Y, et al. Long-term outcomes of patients with symptomatic gastroesophageal reflux disease treated with vonoprazan. Scand J Gastroenterol 2018;53:897-904. doi:10.1080/00365521.2018.1486883
8. Matsueda K, Hongo M, Tack J, Saito Y, Kato H. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. Gut 2012;61:821-828. doi:10.1136/gutjnl-2011-301454
9. Kimura K, Takemoto T. An Endoscopic Recognition of the Atrophic Border and its Significance in Chronic Gastritis. Endoscopy 1969;1:87-97. doi:10.1055/s-0028-1098086
10. Kakuta E, Yamashita N, Katsube T, et al. Abdominal symptom-related QOL in individuals visiting an outpatient clinic and those attending an annual health check. Intern Med 2011;50:1517-1522. doi:10.2169/internalmedicine.50.5390
11. Furuta K, Ishihara S, Sato S, et al. Development and verification of the Izumo Scale, new questionnaire for quality of life assessment of patients with gastrointestinal symptoms. Nihon Shokakibyo Gakkai Zasshi 2009;106:1478-1487.
12. Shinozaki S, Osawa H, Sakamoto H, et al. Timing and Predictors of Recurrence of Dyspepsia Symptoms after Cessation of Acotiamide Therapy for Functional Dyspepsia: A Long-Term Observational Study. Digestion 2020;101:382-390. doi:10.1159/000500134
13. Asaoka D, Nagahara A, Hojo M, et al. Efficacy of a potassium-competitive acid blocker for improving symptoms in patients with reflux esophagitis, non-erosive reflux disease, and functional dyspepsia. Biomed Rep 2017;6:175-180. doi:10.3892/br.2016.828
14. Shinozaki S, Osawa H, Sakamoto H, et al. Adherence to an acotiamide therapeutic regimen improves long-term outcomes in patients with functional dyspepsia. J Gastrointestin Liver Dis 2017;26:345-350. doi:10.15403/jgld.2014.1121.264.ski
15. Sakurai Y, Nishimura A, Kennedy G, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Rising TAK-438 (Vonoprazan) Doses in Healthy Male Japanese/non-Japanese Subjects. Clin Transl Gastroenterol 2015;6:e94. doi:10.1038/ctg.2015.18
16. Masaoka T, Kameyama H, Yamane T, et al. Pathophysiology of Potassium-competitive Acid Blocker-refractory Gastroesophageal Reflux and the Potential of Potassium-competitive Acid Blocker Test. J Neurogastroenterol Motil 2018;24:577-583. doi:10.5056/jnm18036
17. Iwakiri R, Tominaga K, Furuta K, et al. Randomised clinical trial: rabeprazole improves symptoms in patients with functional dyspepsia in Japan. Aliment Pharmacol Ther 2013;38:729-740. doi:10.1111/apt.12444
18. Oshima T, Miwa H. Functional Dyspepsia - A Revolution in Management. Am J Gastroenterol 2018;113:1420-1422. doi:10.1038/s41395-018-0264-8
19. Oshima T, Okugawa T, Tomita T, et al. Generation of dyspeptic symptoms by direct acid and water infusion into the stomachs of functional dyspepsia patients and healthy subjects. Aliment Pharmacol Ther 2012;35:175-182. doi:10.1111/j.1365-2036.2011.04918.x
20. Miwa H, Nakajima K, Yamaguchi K, et al. Generation of dyspeptic symptoms by direct acid infusion into the stomach of healthy Japanese subjects. Aliment Pharmacol Ther 2007;26:257-264. doi:10.1111/j.1365-2036.2007.03367.x
21. Ishii M, Manabe N, Kusunoki H, et al. Real-time evaluation of dyspeptic symptoms and gastric motility induced by duodenal acidification using noninvasive transnasal endoscopy. J Gastroenterol 2008;43:935-941. doi:10.1007/s00535-008-2303-5
22. Ota K, Takeuchi T, Kojima Y, et al. Administration of a standard dose of vonoprazan fumarate delays gastric emptying in Japanese healthy adults: a prospective clinical trial. J Gastroenterol 2021;56:722-731. doi:10.1007/s00535-021-01801-3
23. Shinozaki S, Osawa H, Sakamoto H, Hayashi Y, Kawarai Lefor A, Yamamoto H. The effect of acotiamide on epigastric pain syndrome and postprandial distress syndrome in patients with functional dyspepsia. J Med Invest 2016;63:230-235. doi:10.2152/jmi.63.230
24. Mizuno H, Yamada K, Minouchi K, Kamiyamamoto S, Hinoue Y. Efficacy of vonoprazan for 24-week maintenance therapy of patients with healed reflux esophagitis refractory to proton pump inhibitors. Biomed Rep 2018;8:148-155. doi:10.3892/br.2017.1035