JGH Open An open access journal of gastroenterology and hepatology
Open Access
JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.13023

ORIGINAL ARTICLE

Characteristics of proton pump inhibitor-resistant severe reflux esophagitis and efficacy of vonoprazan in elderly (older than 75 years) and non-elderly groups

Shintaro Hoshino, Eri Momma, Rina Motomiya, Tomohide Tanabe, Mai Koeda, Yoshimasa Hoshikawa, Noriyuki Kawami and Katsuhiko Iwakiri

Department of Gastroenterology, Nippon Medical School, Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan

Key words
elderly, proton pump inhibitor-resistant severe reflux esophagitis, saliva, vonoprazan.

Accepted for publication 6 December 2023.

Correspondence
Katsuhiko Iwakiri, Department of Gastroenterology, Nippon Medical School, Graduate School of Medicine, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.
Email: k-iwa@nms.ac.jp

Declaration of conflict of interest: The authors declare no conflicts of interest.
Author Contribution: Shintaro Hoshino and Katsuhiko Iwakiri designed and conceived this study. Eri Momma, Rina Motomiya, Mai Koeda, Yoshimasa Hoshikawa, Tomohide Tanabe, Noriyuki Kawami, and Katsuhiko Iwakiri collected the data. Shintaro Hoshino and Katsuhiko Iwakiri analyzed and interpreted the results and drafted the manuscript. Shintaro Hoshino and Katsuhiko Iwakiri supported statistical analyses. All authors read and approved the final manuscript.
Financial support: This work was supported by JSPS KAKENHI (Grant Number JP20K082973).

Funding support: JSPS KAKENHI JP20K082973

Abstract

Background and Aim: Previous studies on age differences in proton pump inhibitor (PPI)-resistant reflux esophagitis (RE) have found that stenosis and bleeding complications were significantly more common in the elderly than in the non-elderly. We sought to examine differences between two groups of elderly (75 years or older) and non-elderly (<75 years) patients with (PPI)-resistant severe RE and also the efficacy of vonoprazan (VPZ) in these patients.
Methods: There were 14 patients in the elderly group and 15 in the non-elderly group. Information was obtained on patient background (sex, body mass index [BMI], gastric mucosal atrophy, and the presence of hernia and collagen disease), and all patients underwent the saliva secretion test and esophagogastroduodenoscopy (EGD). The saliva secretion test (amount of saliva secreted, salivary pH, and the acid-buffering capacity) was performed by chewing sugar-free gum for 3 min before EGD. The efficacy of VPZ in both groups was also assessed.
Results: Saliva secretion, sex, BMI, and the presence of gastric mucosal atrophy did not significantly differ between the two groups. The number of hernias larger than 4 cm was significantly higher in the elderly PPI-resistant group, and significantly more patients had collagen disease in the non-elderly group. The efficacy of VPZ was not significantly different between the two groups; however, 10 patients in the non-elderly group had collagen disease, and 4 did not achieve esophageal mucosal healing even with VPZ 20 mg.
Conclusion: The number of large hernias (>4 cm) was significantly higher in the elderly group, while significantly more non-elderly patients had collagen disease. In the non-elderly group with scleroderma, the efficacy of VPZ 20 mg may not be sufficient.

Introduction

Proton pump inhibitor (PPI)-resistant severe reflux esophagitis (RE) is an obstacle to successful treatment of the disease. A previous study compared PPI-resistant and PPI-reactive severe RE and showed that the former was characterized by a female predominance and complicated by collagen disease, and had decreased saliva secretion.[1] Regarding saliva secretion, the involvement of hyposalivation has recently been noted in mild RE and non-erosive reflux disease,[2–5] in addition to PPI-resistant severe RE.

According to clinical practice guidelines for gastroesophageal reflux disease in Japan,[6] potassium-competitive acid blockers (P-CABs) are recommended as the first-line treatment for severe RE and found to achieve esophageal mucosal healing in most cases.[7,8] However, esophageal mucosal healing may also be achieved in 60–70% of severe RE cases with PPI.[9] The basis for drug therapy is mucosal healing at the lowest dose.

Scleroderma is commonly found in patients with PPI-resistant severe RE, particularly non-elderly patients. Previous studies on age differences in PPI-resistant RE have found that stenosis and bleeding complications were significantly more common in the elderly than in the non-elderly.[10] Therefore, a more detailed understanding of age differences in the characteristics of PPI-resistant severe RE is important. To clarify the characteristics of PPI-resistant severe RE in elderly patients (older than 75 years) and non-elderly patients, we examined saliva

secretion, the degree of hiatus hernia (>2 and >4 cm), gastric mucosal atrophy, the presence of collagen disease, sex, and body mass index (BMI) in elderly and non-elderly groups. We also assessed saliva secretion in PPI-resistant severe RE based on the presence or absence of collagen disease. Furthermore, the efficacy of vonoprazan (VPZ) 10 mg for PPI-resistant RE was evaluated.

Methods

This retrospective case–control study was performed at the Nippon Medical School Hospital after obtaining approval (31-04-1119) of the Ethics Committee of the institution.

PPI-resistant severe RE patients older than 75 years (resistant elderly group) and those younger than 75 years (resistant non-elderly group) were recruited at a single center (Department of Gastroenterology, Nippon Medical School Hospital) between August 2018 and December 2022.

All PPI-resistant severe RE patients during this period were enrolled. There were 14 patients in the elderly resistant group and 15 in the non-elderly resistant group. Table 1 shows the backgrounds of both groups. The definition of PPI-resistant severe RE is severe RE before treatment that cannot be healed by the 8-week administration of PPI at the standard dose. The severity of RE was graded based on the Los Angeles Classification,[11] with RE of grade C or D considered to be severe RE.

The present study was conducted on PPI-resistant severe RE at a time point when healing of the esophageal mucosa was controlled by VPZ or when mucosal damage remained after the treatment with VPZ 20 mg. In the present study, patients with PPI-resistant severe RE were initially treated with VPZ 20 mg for 4 weeks, and esophagogastroduodenoscopy (EGD) was performed 4 weeks later (the initial VPZ treatment period). If healing occurred, VPZ 10 mg was administered for 8 weeks as maintenance therapy, and EGD was performed again after 8 weeks. If there was recurrence, VPZ 20 was administered again. If there was no relapse, VPZ 10 mg was continued and the patients were followed up every year. If symptoms worsened, EGD was performed immediately, but this never happened. Since previous studies reported that acid suppressive therapy did not affect saliva secretion,[12,13] we performed our study on PPI-resistant severe RE patients receiving P-CAB therapy.

Patients receiving therapeutic agents with confirmed reduction of saliva secretion, such as antihypertensive agents (anti-adrenergic agents and adrenergic alpha-2 agonists), antidepressants, psychotropic drugs, or anticholinergic drugs, and cigarette smokers[14] were excluded.

A saliva secretion test and EGD were performed. In the saliva secretion test, fasting stimulated saliva secretion was assessed on the day of EGD. This test was performed at approximately 09:00 h before EGD. The amount and pH of stimulated saliva secretion by chewing sugarless gum (CAT 21, J. Morita Corp., Tokyo, Japan) for 3 min were measured. In addition, pH after loading 50 µl of 0.1 N HCl per 0.5 ml of saliva was evaluated as the acid-buffering capacity.[15,16] A Checkbuf System (Morita, Tokyo, Japan) was used to assess pH.

After the collection of saliva, EGD was performed to detect the presence of esophageal mucosal injury, gastric mucosa atrophy, and hernia. The presence of gastric mucosal atrophy was assessed based on the Kimura–Takemoto classification.[17] Patients classified as C1 were considered to have no atrophy. Hiatal hernia was diagnosed if the length between the hiatus and lower margin of the esophageal palisade vessels was >2 or >4 cm.[18] BMI was also measured. Regarding the course of VPZ treatment, previous medical records were reviewed and examined.

Statistical analysis. Data are presented as medians (25th–75th percentiles). Statistical analyses were performed using StatView 5.0 software (SAS Institute, Inc., Cary, NC, USA). The Mann–Whitney *U* test was used to compare differences in BMI, the amount of stimulated saliva secretion, salivary pH, and pH after acid loading (the acid-buffering capacity) in the resistant elderly and non-elderly groups. Fisher's exact test was used to compare sex, the presence of gastric mucosal atrophy, hiatal

Table 1 Clinical characteristics and demographic data of proton pump inhibitor-resistant elderly and non-elderly groups

	Resistant elderly group	Resistant non-elderly group	*P*-value
Number of subjects	14	15	
Sex			
Male/female	2/12	4/11	0.6513†
Esophageal hiatal hernia			
>2 cm (±)	13/1	4/11	>0.9999†
>4 cm (±)	6/8	1/14	0.0352†
Gastric mucosal atrophy			
(±)	1/13	1/14	>0.9999†
BMI	21.1	19.8	
Median (25th–75th percentile)	(19.9–22.8)	(17.9–24.9)	0.4194‡
Collagen disease			
(±)	1/13	10/5	0.0017†

†Statistical analysis by Fisher's exact test.
‡Statistical analysis by Mann–Whitney *U* test.
Gastric mucosal atrophy was classified according to the Kimura–Takemoto classification and closed 1 was regarded as no atrophy.
BMI, body mass index.

hernia, and the healing rate of esophageal mucosal injury by VPZ between the groups. A *P*-value <0.05 was considered significant.

Results

Clinical characteristics. The clinical backgrounds of PPI-resistant elderly and non-elderly groups are shown in Table 1. No significant differences were observed in the sex ratio, BMI, or presence of gastric mucosal atrophy between the two groups. Furthermore, the presence of hernias >2 cm did not significantly differ between the two groups, whereas hernias >4 cm were significantly more in the resistant elderly group. Moreover, significantly more patients had collagen disease in the non-elderly group.

Stimulated saliva secretion. No significant differences were observed in the amount of saliva secretion, salivary pH, or the acid-buffering capacity between the groups (Table 2).

Efficacy of VPZ in PPI-resistant elderly and non-elderly groups. Among the 14 patients in the resistant elderly group, 5 treated with VPZ 20 mg and 9 treated with VPZ 10 mg achieved esophageal mucosal healing. In the non-elderly group, esophageal mucosal healing was not achieved in 4 out of the 15 patients treated with VPZ 20 mg. Of the remaining 11 patients, 6 treated with VPZ 20 mg and 5 treated with VPZ 10 mg achieved esophageal mucosal healing. A comparison of the esophageal mucosal healing rates of VPZ between the resistant elderly and non-elderly groups revealed no significant difference ($P = 0.0996$). Ten patients in the non-elderly group had collagen disease, and four did not achieve esophageal mucosal healing even with VPZ 20 mg.

Discussion

The number of hernias >4 cm was significantly higher in the resistant elderly group. No significant differences were observed in other factors. Hernias >2 cm are generally considered to be significant; however, no significant differences were observed in the number of hernias ≥2 cm in both groups. A diagnosis of hernia, which is the distance from the diaphragm to the lower end of the palisade vessels, is typically made during deep inspiration. A hernia of 2 cm after deep inspiration is a physiological hernia because the diaphragm moves approximately 2 cm downward during deep inspiration, as assessed by high-resolution manometry.[18] A diagnosis with deep aspiration is useful for detecting Barrett's mucosa and esophageal mucosal injury, whereas for hernias a length of ≥4 cm at deep inspiration is considered to be significant.

Previous studies have reported that significantly more females had PPI-resistant severe RE than PPI-responsive severe RE.[1] When patients with PPI-resistant severe RE was divided by age, 12 out of 14 in the resistant elderly group and 11 out of 16 in the non-elderly group were female. Although there were more females with PPI-resistant severe RE, no significant difference was observed between the two groups.

Esophageal motility did not significantly differ between patients with PPI-resistant and PPI-responsive severe RE in a previous study,[1] and the motility pattern was similar in both groups (ineffective esophageal motility or absent motility).[19] Even for PPI-resistant severe RE, the motility pattern was similarly impaired. Therefore, since the aim of the present study was to compare age differences in PPI-resistant severe RE, esophageal motility was not examined.

On the other hand, significantly more patients in the resistant non-elderly group had collagen disease (mainly scleroderma): 10 out of 16 patients in this group and only 1 out of 12 in the resistant elderly group.

The presence of a large hernia in the resistant elderly group is associated with the appearance of an acid pocket (acid layer)[20,21] in the hernia during the postprandial period and a high rate of acid reflux during transient lower esophageal sphincter (LES) relaxation,[22] which is the major mechanism of acid reflux.[23–25] In addition, LES pressure is expected to be low, which increases acid reflux due to low LES pressure because many resistant RE patients have severe RE and a large hernia.[26]

Regarding the higher frequency of PPI-resistant severe RE in the resistant non-elderly group with scleroderma, we initially considered low saliva secretion to be a causative factor. Although the present study was conducted on a small number of cases, no significant differences were observed in saliva secretion when PPI-resistant severe RE was divided according to the presence or absence of collagen disease (mainly scleroderma). However, saliva secretion was negligible in some cases. Therefore, further studies are warranted.

Based on the present results, there are two patterns of PPI-resistant severe RE. The presence of a large hernia (≥4 cm) in the resistant elderly group and collagen disease in the resistant non-elderly group are closely related to the pathogenesis of PPI resistance. In the future, we intend to examine the characteristics of PPI-resistant severe RE that cannot be healed without P-CABs because 60–70% of severe RE cases are successfully treated with PPIs.[9]

Regarding the treatment of PPI-resistant severe RE, the elderly group, in which large hernias (>4 cm) were more common, was healed by VPZ. Excessive esophageal acid exposure due to large hernias significantly contributed to the pathogenesis

Table 2 Stimulated saliva secretion in the proton pump inhibitor-resistant elderly and non-elderly groups

	Resistant elderly group	Resistant non-elderly group	*P*-value
Amount of stimulated saliva (mL) secretion	3.7 (2.2–4.4)	4.1 (1.9–6.6)	0.8786
Salivary pH	7.0 (6.6–7.2)	6.9 (6.7–7.3)	0.8571
Salivary pH after acid loading (acid-buffering capacity)	5.9 (5.5–6.2)	5.5 (5.3–5.9)	0.2578

Data expressed as median (25th–75th percentile). Statistical analysis by Mann–Whitney *U* test.

of PPI-resistant severe RE in the elderly group. However, patients with large hernias in this group were all healed by VPZ. Furthermore, the less frequent complication of collagen disease in the elderly group may be attributed to many patients with collagen disease (mainly scleroderma) not living up to 75 years or more.

Another important result of the present study is that 40% of the patients with collagen disease were not healed even with VPZ. Moreover, collagen disease needs to be considered in non-elderly patients with PPI-resistant severe RE. Vascular complications have been reported in scleroderma patients,[27] which may be related to esophageal mucosal injury.

The healing rate with VPZ was low in patients with scleroderma in the non-elderly group; therefore, VPZ did not appear to adequately suppress acid secretion in these patients. We previously monitored intragastric pH in two patients with VPZ 20 mg-resistant RE and scleroderma while receiving treatment with VPZ 20 mg.[7] The findings showed that the percentage time of intragastric pH >4 was in the latter half of 40%. This percentage time of intragastric pH > 4 was markedly less than that observed with the normal use of VPZ 20 mg.[28] Since VPZ is metabolized by CYP3A4, a drug interaction with CYP3A4 may have affected the results obtained. Although the number of patients not healed by VPZ was small, this issue warrants further study.

There are some limitations that need to be addressed. This was a retrospective analysis of a small number of cases at a single institution. Nevertheless, this is the first study to characterize PPI-resistant severe RE based on age differences. Prospective studies at multiple centers are needed in the future.

In conclusion, the PPI-resistant elderly group is characterized by the presence of hernias >4 cm and a lower prevalence of collagen disease (mainly scleroderma) than the resistant non-elderly group. VPZ was effective for all patients in the elderly group but may not be adequate for some in the non-elderly group, particularly those with collagen disease.

Acknowledgment

We would like to thank Medical English Service for English language editing.

Patient consent

Written informed consent was waived owing to the retrospective design of this study.

Data availability statement. All relevant data are within the manuscript. Further enquiries may be directed to the corresponding author.

References

1 Tanabe T, Koeda M, Kitasako Y *et al*. Stimulated saliva secretion is reduced in proton pump inhibitor-resistant severe reflux esophagitis patients. *Esophagus*. 2021; **18**: 676–83.
2 Koeda M, Tanabe T, Kitasako Y *et al*. Saliva secretion is reduced in proton pump inhibitor-responsive non-erosive reflux disease patients. *Esophagus*. 2021; **18**: 900–7.
3 Koeda M, Tanabe T, Kitasako Y *et al*. Saliva secretion is reduced in mild reflux esophagitis patients. *Esophagus*. 2022; **19**: 351–9.
4 Koeda M, Momma E, Tanabe T *et al*. Differences in salivary secretion and epidermal growth factor concentrations in mild reflux esophagitis and non-erosive reflux disease. *Esophagus*. 2023; **20**: 317–24.
5 Momma E, Koeda M, Hoshikawa Y *et al*. Saliva secretion is significantly lower in female patients with mild reflux esophagitis than in female healthy controls. *Digestion*. 2023; **104**: 299–305.
6 Iwakiri K, Fujiwara Y, Manabe N *et al*. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2021. *J. Gastroenterol.* 2022; **57**: 267–85.
7 Hoshino S, Kawami N, Takenouchi N *et al*. Efficacy of vonoprazan for proton pump inhibitor-resistant reflux esophagitis. *Digestion*. 2017; **95**: 156–61.
8 Ashida K, Sakurai Y, Hori T *et al*. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Aliment. Pharmacol. Ther.* 2016; **43**: 240–51.
9 Mizuno H, Matsuhashi N, Sakaguchi M *et al*. Recent effectiveness of proton pump inhibitors for severe reflux esophagitis: the first multicenter prospective study in Japan. *J. Clin. Biochem. Nutr.* 2015; **57**: 233–8.
10 Sakaguchi M, Manabe N, Ueki N *et al*. Factors associated with complicated erosive esophagitis: a Japanese multicenter, prospective, cross-sectional study. *World J. Gastroenterol.* 2017; **23**: 318–27.
11 Lundell LR, Dent J, Bennett JR *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut*. 1999; **45**: 172–80.
12 Namiot Z, Stasiewicz J, Kralisz M *et al*. Omeprazole therapy and salivary flow rate in duodenal ulcer patients. *Med. Sci. Monit.* 2001; **7**: 276–81.
13 Hoshikawa Y, Momma E, Hoshino S *et al*. Proton pump inhibitor treatment has little effects on secretion of saliva in patients with proton pump inhibitor-responsive mild reflux esophagitis and non-erosive reflux disease. *Digestion*. 2023; **104**: 187–92.
14 Konturek JW, Bielanski W, Konturek SJ, Bogdal J, Oleksy J. Distribution and release of epidermal growth factor in man. *Gut*. 1989; **30**: 1194–200.
15 Kitasako Y, Moritsuka M, Foxton RM, Ikeda M, Tagami J, Nomura S. Simplified and quantitative saliva buffer capacity test using a hand-held pH meter. *Am. J. Dent.* 2005; **18**: 147–50.
16 Moritsuka M, Kitasako Y, Burrow MF, Ikeda M, Tagami J. The pH change after HCl titration into resting and stimulated saliva for a buffering capacity test. *Aust. Dent. J.* 2006; **51**: 170–4.
17 Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy*. 1969; **3**: 87–97.
18 Hanada Y, Hoshino S, Hoshikawa Y *et al*. Endoscopic diagnosis of hiatus hernia under deep inspiration is not consistent with esophageal manometric diagnosis. *J. Gastroenterol.* 2018; **53**: 712–7.
19 Yadlapati R, Kahrilas PJ, Fox MR *et al*. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0©. *Neurogastroenterol. Motil.* 2021; **33**: e14058.
20 Fletcher J, Wirz A, Young J, Vallance R, McColl KEL. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. *Gastroenterology*. 2001; **121**: 775–83.
21 Kahrilas PJ, McColl K, Fox M *et al*. The acid pocket: a target for treatment in reflux disease? *Am. J. Gastroenterol.* 2013; **108**: 1058–64.
22 Beaumont H, Bennink RJ, de Jong J, Boeckxstaens GE. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. *Gut*. 2010; **59**: 441–51.

23 Dent J, Dodds WJ, Friedman RH *et al*. Mechanism of gastroesophageal reflux in recumbent asymptomatic subjects. *J. Clin. Invest.* 1980; **65**: 256–67.
24 Iwakiri K, Hayashi Y, Kotoyori M *et al*. Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of gastroesophageal reflux but are not the cause of reflux disease. *Dig. Dis. Sci.* 2005; **50**: 1072–7.
25 Iwakiri K, Kawami N, Sano H *et al*. Mechanisms of excessive esophageal acid exposure in patients with reflux esophagitis. *Dig. Dis. Sci.* 2009; **54**: 1686–92.
26 Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? *Ann. Intern. Med.* 1992; **117**: 977–82.
27 Sakkas LI. New developments in the pathogenesis of systemic sclerosis. *Autoimmunity*. 2005; **38**: 113–6.
28 Jenkins H, Sakurai Y, Nishimura A *et al*. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment. Pharmacol. Ther.* 2015; **41**: 636–64.