—Review—

Treatment Strategy for Standard-Dose Proton Pump Inhibitor-Resistant Reflux Esophagitis

Katsuhiko Iwakiri

Department of Gastroenterology, Nippon Medical School, Graduate School of Medicine, Tokyo, Japan

Reflux esophagitis is characterized by excessive esophageal acid exposure. To treat reflux esophagitis, it is necessary to reduce excessive esophageal acid exposure to within the normal range. The first-line drug for the treatment of reflux esophagitis is a standard-dose proton-pump inhibitor (PPI), which is also recommended by the Evidence-based Clinical Practice Guidelines 2015 for gastroesophageal disease of the Japanese Society of Gastroenterology. It has been reported that the response to a standard dose of PPI in patients with mild reflux esophagitis is 90−100%, and that in patients with severe reflux esophagitis is 80−85%. However, PPI-resistant reflux esophagitis has been increasing. When the standard dose of PPI is not effective, modification of the lifestyle with PPI therapy, switching to another PPI, or a change in the administration method (before meals), as well as double-dose PPI (in divided doses), may be effective. In addition, vonoprazan (potassium-competitive acid blocker), which has rapid and potent acid-suppressive effects, became available in February 2015 in Japan. In the clinical trial data, vonoprazan is very effective for reflux esophagitis. However, clinical data on vonoprazan are still insufficient. The establishment of a new treatment for reflux esophagitis taking advantage of the rapid and potent acid-suppressive effects is awaited. (J Nippon Med Sch 2017; 84: 209−214)

Key words: reflux esophagitis, proton-pump inhibitor (PPI), PPI-refractory reflux esophagitis, esophageal motility, potassium-competitive acid blocker (P-CAB)

Introduction

The cause of esophageal mucosal breaks in reflux esophagitis is excessive esophageal acid exposure, and the duration of esophageal acid exposure significantly increases with the severity of reflux esophagitis[1]. Esophageal mucosal break can be healed by normalizing (≤4%) excessive esophageal acid exposure. Endoscopic healing can be achieved in 90−100 and 80−85% of patients with mild and severe reflux esophagitis, respectively, by standard-dose oral PPI therapy, which is the first-line treatment for GERD[2,3]. However, according to a report in 2015, the endoscopic healing rate by PPI (primarily standard-dose PPI) therapy decreased to about 70 and 60% in grade C and grade D reflux esophagitis, respectively, based on the LA classification, and the prevalence of severe reflux esophagitis that cannot be healed with standard-dose PPI is increasing[4]. This review gives an overview of treatments for standard-dose PPI-resistant reflux esophagitis.

Treatments for Standard-dose PPI-resistant Reflux Esophagitis

1) Modification of lifestyle

According to the evaluation of acid reflux by the long-term measurement of the esophageal pressure and pH, acid reflux is more often caused by transient LES relaxation than by a low LES pressure[5−8]. Transient LES relaxation is LES relaxation unaccompanied by swallowing, which is the mechanism of belching and is not a morbid reaction[9] (**Fig. 1**). During transient LES relaxation, reflux of only air or both air and acid occurs. Transient LES relaxation is likely to occur: (1) under stimulation to induce extension of the gastric fundus, i.e., overeating or swallowing of air associated with eating too quickly, and (2) on ingestion of a high-fat meal[9]. Slow eating, and avoiding overeating and high-fat meals are important measures to reduce the frequency of transient LES relaxation. In addition, because acid reflux frequently occurs within

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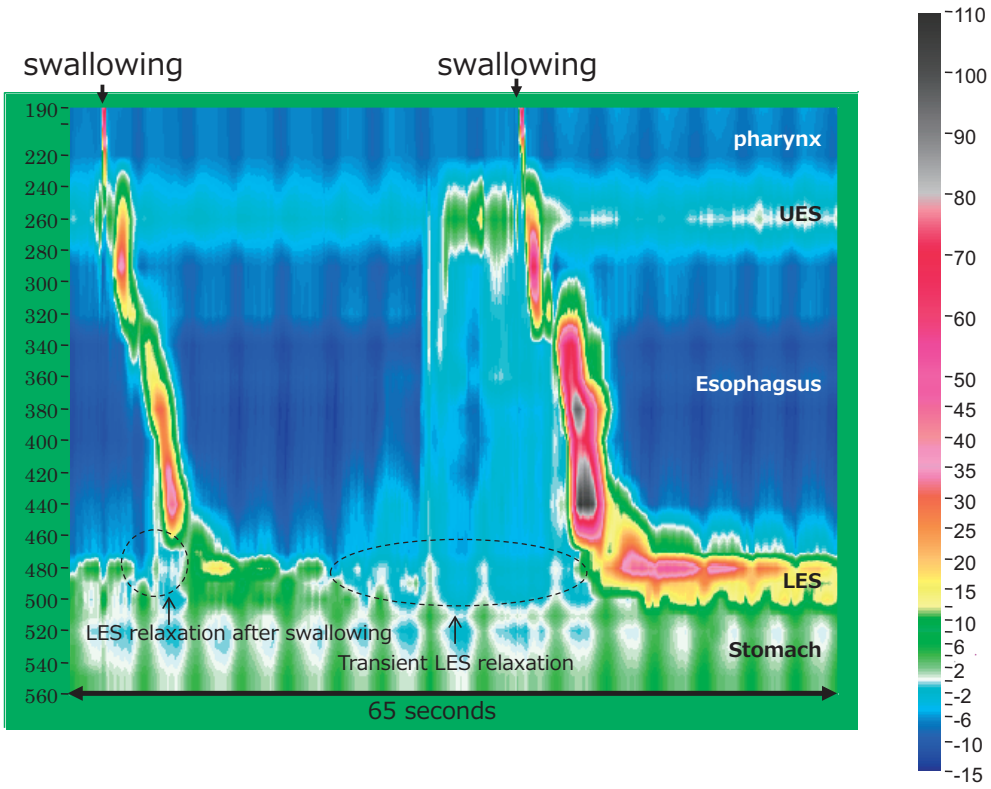

Fig. 1 High-resolution manometric findings of LES relaxation after swallowing and transient LES relaxation. LES relaxation with short duration of about 5 seconds (the left side of the figure) and prolonged (about 30 seconds) LES relaxation (the middle of the figure) after swallowing. There is no pharyngeal swallowing signal before or after the onset of prolonged LES relaxation. Therefore, this prolonged LES relaxation is transient LES relaxation. LES: lower esophageal sphincter, UES: upper esophageal sphincter.

3 hours after a meal, going to bed shortly after eating increases the risk of acid reflux during sleep. Therefore, it is also important to avoid eating soon before going to bed (3–4 hours)[10]. Since the frequency of transient LES relaxation has been reported to increase significantly with the body mass index (BMI)[11], it can be reduced in overweight (BMI≥25) persons by losing weight. The quality of life (QOL) has been reported to be improved by such modifications of lifestyle in addition to PPI therapy[12].

2) Reducing the occurrence of acid reflux

Since transient LES relaxation is the primary mechanism of acid reflux, the excessive esophageal acid exposure can be reduced by decreasing the frequency of transient LES relaxation. Baclofen, a GABA-B agonist, is a drug clinically available for reducing the frequency of transient LES relaxation[13–15]. However, considering that the use of baclofen for the treatment of reflux esophagitis is off-label use for the purpose of coverage by the national health insurance scheme, that it has been reportedly used at higher doses abroad than in Japan, and that it has central nervous system side effects, suppression of the frequency of transient LES relaxation with baclofen is not practical.

While there is no difference in the frequency of transient LES relaxation between healthy subjects and GERD patients[5–8] (**Table 1**), the frequency of acid reflux during transient LES relaxation is significantly greater in GERD patients than in healthy subjects[5–8] (**Table 2**). Therefore, the cause of excessive esophageal acid exposure in patients with reflux esophagitis is not the high frequency of transient LES relaxation but the higher rate of acid reflux during transient LES relaxation.

With regard to the difference in proportion of acid reflux during TLESR, it is considered that the location of the acid pocket, which is the layer of acid that appears postprandially above the dietary layer immediately below the esophagogastric junction (EGJ) as a source of postprandial acid reflux is very important[16–18]. When the acid pocket is located in the hernia sac (supradiaphragmatic location), the proportion of acid reflux episodes

Table 1 Frequency of transient lower esophageal sphincter (LES) relaxation (a 3-hour postprandial period)

Healthy subjects	NERD	Mild RE	Severe RE			References
4.5/hour (3.7-5.7)			5.0 (3.3-6.7)	N.S.	Median (interquartile range)	Iwakiri, et al. Ref 5
5.0/hour (4.3-6.3)			4.7 (3.3-5.7)	N.S.	Median (interquartile range)	Hayashi, et al. Ref 6
6.7/hour (5.3-8.0)		5.7 (4.1-6.2)	5.3 (4.3-6.0)	N.S.	Median (interquartile range)	Iwakiri, et al. Ref 7
6.5/hour (0.5)	5.1 (0.5)	4.9 (0.4)		N.S.	Mean (SEM)	Sano, et al. Ref 8

NERD: non-erosive refluxesophagitis, RE: reflux esophagitis, NS: not significant

Table 2 Frequency of acid reflux during transient lower esophageal sphincter (LES) relaxation in the sitting position (a 3-hour postprandial period)

Healthy subjects	NERD	Mild RE	Severe RE		Esophageal pH measurement site	References
10.9% (0-18.8%)			48.1% * (27.2-71.4%)	Median (interquartile range)	7 cm above the LES	Iwakiri, et al. Ref 5
9.2% (0-13.3%)			42.7% * (27.3-76.2%)	Median (interquartile range)	5 cm above the LES	Hayashi, et al. Ref 6
11.8% (1.8-20.3%)		35.7% * (17.1-47.3%)	50.9% * ** (29.4-70.0%)	Median (interquartile range)	7 cm above the LES	Iwakiri, et al. Ref 7
10.8% (0.5)	42.3% * ** (4.8)	28.0% * (3.8)		Mean (SEM)	7 cm above the LES	Sano, et al. Ref 8

NERD: non-erosive refluxesophagitis, RE: reflux esophagitis, NS: not significant
*p<0.05 vs healthy subjects, **p<0.05 vs mild RE

during TLESR (70−85%) is significantly higher than when it is located below the diaphragm (7−20%)[18].

3) Improving the esophageal acid clearance

In patients who show delayed esophageal acid clearance, the duration of excessive esophageal acid exposure can be reduced by improving the esophageal acid clearance. According to our evaluation, there was no clear difference in primary peristalsis, which is important for esophageal acid clearance, between in patients with mild reflux esophagitis and healthy subjects[7,19], but mild abnormalities of peristaltic activity may be observed in individual patients. In such patients, peristaltic activity may be improved by the administration of gastrointestinal prokinetic drugs[20]. On the other hand, the esophageal acid clearance is markedly delayed in patients with severe reflux esophagitis, but the effect of the administration of gastrointestinal prokinetic drugs is limited.

4) Acid control

Although excessive esophageal acid exposure is the cause of reflux esophagitis[1], drugs are not expected to reduce the frequency of acid reflux or improve the esophageal acid clearance in patients with severe reflux esophagitis. Therefore, the control of gastric acid is important to reduce the duration of esophageal acid exposure.

4-1) Switching to another PPI

While the endoscopic healing rate of reflux esophagitis by standard-dose PPI therapy is similar among various PPI, individual variation is observed in the efficacy of PPI. When lansoprazole and omeprazole are administered to the same patient, the suppressive effect on acid secretion markedly differs between the two PPI. Therefore, if the response to PPI therapy is insufficient, it is important to identify the optimal PPI for each patient by switching to another PPI[21]. These differences in the effect among PPI are related to the differences in the degree of dependence on CYP2C19, which is involved in their metabolism.

4-2) Changing the administration method of PPI

Proton pumps are present on the membranes of tubulovesicles in the cytoplasm when parietal cells are resting, but tubulovesicles migrate towards the membranes of secretory canaliculi when parietal cells sense stimuli for acid secretion, such as a meal, and acid is secreted from the proton pumps that appear on the membranes of

secretory canaliculi. PPI are activated by acid in the secretory canaliculi, and acid secretion is suppressed as activated PPI bind covalently with proton pumps on the membranes of secretory canaliculi. To maximize the effect of a PPI, it is necessary to set its peak circulating concentration after a meal. Since the blood concentration of PPI reaches a peak 2–3 hours after oral administration, it is considered effective to administer PPI 1 hour before a meal[22]. In addition, it is effective to administer PPI before dinner[23], because the largest number of proton pumps appear on the membranes of secretory canaliculi after dinner, which is generally the most substantial meal of the day.

4-3) Changing the dose of PPI

Even when endoscopic healing cannot be achieved with a standard dose of PPI, reflux esophagitis, which is caused by excessive esophageal acid exposure, is healed by more potent suppression of acid secretion with double dose PPI. In double-dose PPI therapy, it is more effective to administer in divided doses rather than in a single dose[24]. Splitting the dose and, thus, creating a bimodal distribution of the plasma PPI concentration is more advantageous, (1) because PPI in the secretory canaliculi activated by gastric acid are rapidly deactivated and acid secretion from proton pumps on the membranes of secretory canaliculi which appear after the plasma PPI concentration disappears about 10–12 hours after administration of PPI is not suppressed, and (2) because about 25% of the proton pumps are newly produced daily[25].

4-4) Switching to vonoprazan

In February 2015, vonoprazan, which is a novel acid secretion-inhibitory drug, became available. While vonoprazan targets proton pumps similarly to PPI, it competitively inhibits the binding of the proton pump to potassium ions and belongs to a new category (potassium-competitive acid blocker) different from PPI. Characteristics of vonoprazan are the rapid onset, high potency, and long duration of its acid secretion-inhibitory effect[25,26]. Excellent results have also been reported by its clinical trials against reflux esophagitis[28,29]. However, there is also concern over adverse effects associated with its strong acid-suppressive effect.

Although there have been only a few reports on the clinical use of vonoprazan against reflux esophagitis, endoscopic healing was observed in 88.5% of the patients with PPI-resistant reflux esophagitis treated at our department (including those with refractory reflux esophagitis complicating scleroderma) by the 4-week administration of 20 mg vonoprazan, clearly indicating a therapeutic effect against PPI-resistant reflux esophagitis[30]. Moreover, after healing, mucosal remission could be maintained in 76.5% of the patients with 10 mg vonoprazan, suggesting its strong suppressive effect on acid secretion[30].

Treatment of Mild Reflux Esophagitis with Vonoprazan

In severe reflux esophagitis, maintenance therapy is recommended after the initial treatment regardless of the presence or absence of symptoms for the prevention of recurrence and complications, as described in the guidelines[31]. However, in the management of mild reflux esophagitis, which is rarely exacerbated[32,33] the control of acid reflux symptoms is the most important while it is necessary to confirm the absence of aggravation by periodic endoscopic follow-ups. Since 3–5 days are necessary until a stable acid secretion-inhibitory effect is achieved with PPI, continuous PPI therapy is necessary. However, with the oral administration of 20 mg vonoprazan, the intragastric pH becomes ≥4 after 2.5 hours and remains at pH ≥4 for nearly 24 hours thereafter[26,27]. Because of these characteristics of the inhibitory effect of 20 mg vonoprazan on acid secretion, 20 mg vonoprazan is considered to be suited for on-demand therapy. Since vonoprazan is not a PPI, we consider that a new regimen for mild reflux esophagitis and non-erosive reflux disease (NERD) that makes the most of the characteristics of 20 mg vonoprazan should be established rather than inheriting the regimen using PPI.

Conclusion

To manage standard-dose PPI-resistant reflux esophagitis, modification of lifestyle, change to another PPI, change of the administration method, and double-dose PPI in divided doses are effective measures. Change of PPI to vonoprazan is also effective. Since vonoprazan is a novel acid-suppressive drug with an action mechanism different from that of PPI, the establishment of a new regimen for reflux esophagitis and NERD that makes the most of its characteristics (rapid and potent inhibition of acid secretion) is awaited.

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