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Review

Potent Potassium-competitive Acid Blockers: A New Era for the Treatment of Acid-related Diseases

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Conventional proton pump inhibitors (PPIs) are used as a first-line therapy to treat acid-related diseases worldwide. However, they have a number of limitations including slow onset of action, influence by cytochrome P450 polymorphisms, unsatisfactory effects at night, and instability in acidic conditions. Alternative formulations of conventional PPIs have been developed to overcome these problems; however, these drugs have only introduced small advantages for controlling acid secretion compared to conventional PPIs. Potassium-competitive acid blockers (P-CABs) were developed and have beneficial effects including rapid, long-lasting, and reversible inhibition of the gastric hydrogen potassium ATPase, the proton pump of the stomach. Vonoprazan was recently innovated as a novel, orally active P-CAB. It is currently indicated for the treatment of gastric and duodenal ulcers, reflux esophagitis, and prevention of low-dose aspirin- or nonsteroidal anti-inflammatory drug-related gastric and duodenal ulcer recurrence in Japan. Vonoprazan does not require enteric coating as it is acid-stable, and it can be taken without food because it is quickly absorbed. Vonoprazan accumulates in parietal cells under both acidic and neutral conditions. It does not require an acidic environment for activation, has long-term stability at the site of action, and has satisfactory safety and tolerability. Thus, vonoprazan may address the unmet medical need for the treatment of acid-related diseases.
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Key Words
Anti-inflammatory agents, non-steroidal; Esophagitis; H^+, K^+-exchanging ATPase; *Helicobacter pylori*; Potassium-competitive acid blocker

Introduction

Proton pump inhibitors (PPIs) have often been used for acid-related diseases including gastroesophageal reflux disease (GERD), gastric and duodenal ulcers, non-steroidal anti-inflammatory drug (NSAID)-associated ulcers, and *Helicobacter pylori* eradication therapy. Conventional PPIs with a benzimidazole structure irreversibly inhibit hydrogen potassium (H^+, K^+)-ATPases, which produce acid in gastric parietal cells and more strongly block acid secretion compared to histamine H2 receptor antagonists.[1-3] Although PPIs have been used for more than a quarter-century as a first-line treatment for these diseases, it has become clear that there are some issues in need of improvement (Table 1).[4] First, it takes several days to show maximal effect.[5-7] Reflux symptoms of GERD are not sufficiently relieved after the first dose of PPIs in two-thirds

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Table 1. Comparison of Potassium-competitive Acid Blocker and Proton Pump Inhibitor

	P-CAB (vonoprazan)	PPI
Maximal acid suppression after dosing (day)[7]	1	3-5
Influence of CYP2C19 polymorphisms[10,11,34,45,46,48,49]	-	+
Influence of meal[15,42]	-	+
Stability in acidic conditions[15]	>	
Acid suppression at night (pH 4 HTR) (mean ± SD, %)[48]	67.9 ± 28.3 vs 12.9 ± 10.9 (E) 84.3 ± 20.3 vs 15.3 ± 13.3 (R)	
H. pylori eradication rate (first-line triple therapy) (%)[61]	92.6	75.9 (L)
Healing rate of sever reflux esophagitis (LA, Grade C/D) (%)[49,91]	88.0-96.0	53.9-82.6 (L)
PPI-refractory GERD[92,93]	>	

P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; HTR, holding time ratio; LA, Los Angeles; GERD, gastroesophageal reflux disease; CYP, cytochrome P450; E, esomeprazole; L, lansoprazole; R, rabeprazole; >, P-CAB is better than PPI.

of patients because of its slow onset of the action,[8,9] and one-half of patients still have symptoms even after 3 days of treatment.[9] Second, the effects of PPIs are influenced by cytochrome P450 (CYP) 2C19 polymorphism.[10,11] Third, its effects at night are not satisfactory.[12-14] Finally, although it requires an acidic environment for activation, PPIs are unstable in acidic conditions,[15] so enteric coating is needed.

To overcome the aforementioned unmet needs, alternative formulations of conventional PPIs and new H^+, K^+-ATPase inhibitors have been established. With these efforts, vonoprazan (TAK-438), a potassium-competitive acid blocker (P-CAB), was developed. It was found to have satisfactory effects and a good safety profile in clinical studies of gastric and duodenal ulcers, reflux esophagitis, NSAID-associated ulcers, and *H. pylori* eradication. Vonoprazan (Takecab) was released to the market in Japan in February 2015. In this review, we summarize the effects of P-CABs, mainly using vonoprazan data.

Alternative Formulation of Conventional Proton Pump Inhibitors

Immediate-release omeprazole and dexlansoprazole modified release (MR), which improve nocturnal acid breakthrough (NAB), have been introduced as alternative formulations of PPIs in some countries.[16,17] Dexlansoprazole MR is the R-enantiomer of lansoprazole and is a PPI with dual delayed-release formulation.[18] The dual release system in the duodenum and small intestine achieved 2 peak concentrations within 2 hours and 5 hours after administration.[19] Percentage time 24-hour intragastric pH above 4 of dexlansoprazole MR 60 mg and lansoprazole 30 mg once daily for 5 days administration was 71% and 60%, respectively ($P < 0.01$).[20] However, these drugs only have small advantages for the control of acid secretion compared to conventional PPIs.[20]

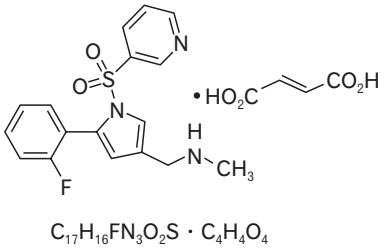

Figure 1. Chemical structure of vonoprazan.

Development of Potassium-competitive Acid Blockers

P-CABs were first developed in the 1980s,[21] and have been studied by many pharmaceutical companies worldwide, as they rapidly, effectively, and reversibly inhibit the proton pump (H^+,K^+-ATPase α subunit).[22] However, P-CABs such as the imidazopyridine compound SCH28080 from Schering-Plough Corporation have an imidazopyridine ring that correlated with hepatic toxicity in human clinical studies and did not show superior effects compared to conventional PPIs. Imidazopyridine derivatives including AR-H047108,[23-25] and linaprazan (AZD0865), imidazonaphthyridine derivatives including soraprazan,[26] pyrimidine derivatives including revaprazan (YH1885), and pyrrole derivatives including vonoprazan (TAK-438) (Fig. 1) were also developed. However, only revaprazan and vonoprazan are currently on the market (Table 2). A concentration of up to 75 mg linaprazan provided similar efficacy to 40 mg esomeprazole for the healing of reflux esophagitis and controlling of heartburn.[27] However, linaprazan did not provide more clinical benefits than 20 mg esomeprazole for the management of GERD.[28] Because linaprazan had similar effects to esomeprazole but caused hepatic toxicity, its development was discontinued. Revaprazan is only available in South Korea and India, and is used for the treatment of peptic ulcers but not for GERD. Revaprazan rapidly inhibits gastric acid secretion but intragastric pH could only be increased to a maximum of 5 at the dosage used.[29] The P-CAB YH4808 was developed in Korea; dosage ≥ 200 mg produces a

Table 2. Drugs in the Market and the Trials

Drug	Phase
Revaprazan (YH1885)	Market (2007 South Korea, India)
Vonoprazan (TAK-438)	Market (2015 Japan)
	Phase III (Asia)
	Phase IIb (EU)
Tegoprazan (RQ-4)	Phase III (South Korea)
	Phase I (Japan)
YH4808	Phase II (South Korea)
DWP14012	Phase II (South Korea)
KFP-H008	Preclinical (China)

rapid, sustained suppression of gastric secretion with good tolerability.[30] The twice-daily use of YH4808 is more effective, especially at night, than the same dose used once-daily.[30] However, this compound is still not available clinically. Other agents, DWP14012, and 1-(5-(1H-indol-5-yl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl)-N-methylmethanamine (KFP-H008), P-CABs, are under development.[31,32] Tegoprazan is another potent P-CAB[33] that was successfully tested in a phase III trial in Korea and will be released to the market in 2018 (Table 2). A compound that has a pyrrole derivative in the center was found through high-throughput screening.[34] After modifying the compound to reduce hepatic toxicity and influence of CYP2C19 polymorphism, vonoprazan was developed.[35]

Vonoprazan

Pharmacokinetics

Vonoprazan is a novel, orally active P-CAB that binds and inhibits H^+, K^+-ATPase at the final step in the acid secretory pathway in gastric parietal cells, and it has different mechanisms of action than conventional PPIs. It can inhibit the proton pump, even in neutral environments with an inhibitory constant (Ki) of 10 nM at pH 7 and of 3 nM at pH 6.5.[36] It has stronger potential to inhibit the gastric proton pump than another P-CAB, SCH28080, and lansoprazole. The half-maximal inhibitory concentrations of vonoprazan, SCH28080, and lansoprazole were 0.018 nM, 0.14 nM, and 7.6 μM, respectively.[36] The half-life ($T_{1/2}$) of vonoprazan dissociation by potassium chloride was 12.5 hours in isolated proton pumps, and that of SCH28080 was less than 2 minutes. Therefore, vonoprazan has high affinity and slow clearance from gastric parietal cells, accumulating in both resting and stimulated conditions.[37,38] The acid dissociation constant of vonoprazan is 9.37, which is higher than that of conventional PPIs and other P-CABs.[39]

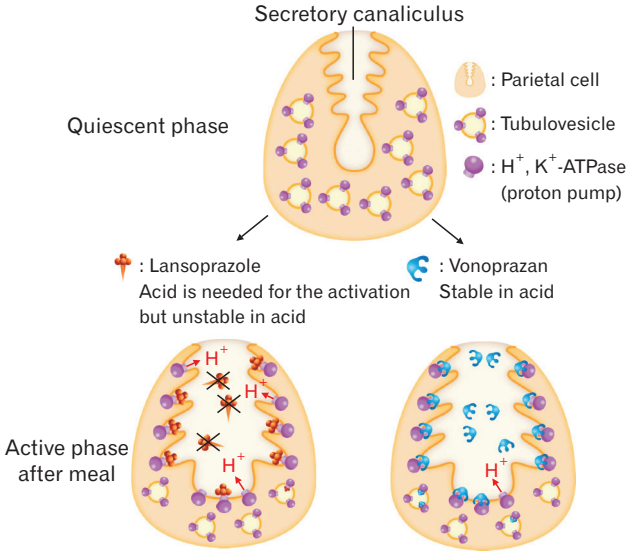

Figure 2. Comparison of mechanisms of action of lansoprazole (conventional proton pump inhibitor) and vonoprazan (potassium-competitive acid blocker). Hydrogen potassium (H^+, K^+)-ATPases are located in tubulovesicles in quiescent phage and appear on the apical membrane of secretory canaliculus in the active phase, which occurs after a meal. Lansoprazole converts to its active form in the secretory canaliculus, though it degrades soon after (X). The active form of lansoprazole covalently binds to H^+, K^+-ATPase (proton pump). Vonoprazan stably accumulates in the acidic secretory canaliculus and non-covalently binds to H^+, K^+-ATPase with very a very slow dissociation rate and can inhibit newly exposed H^+, K^+-ATPase for a long time.

When vonoprazan is exposed to acidic conditions, it is instantly protonated and remains stable. It can accumulate, function, and bind the proton pump of gastric parietal cells in strongly acidic secretory canaliculi. Vonoprazan binds ~10 Å from the ion binding site that is close to the middle of the membrane domain of H^+, K^+-ATPase. Hydrogen bonding between Tyr799 and the sulfone of vonoprazan was suggested.[36] The dissociation rate of vonoprazan from H^+, K^+-ATPase is slow and acid does not decomposed it. Non-ionic type of vonoprazan is decreased in a strong acidic secretory canaliculi and passive transport from the acidic secretory canaliculus to the cytoplasm is inhibited. It is therefore retained for a long time inside the parietal cells and can inhibit H^+, K^+-ATPase that is activated by further stimulation of acid secretion (Fig. 2).[15,36,40] The concentration of vonoprazan is up to 10^8-fold higher in the secretory canaliculus of the parietal cell than in the plasma. It can stay in the protonated form, and binds to the H^+, K^+-ATPase α subunit to compete with potassium binding, and inhibits the function of the pump.[41] The binding of vonoprazan to the proton pump is ionic, and its effects are reversible and dose-dependent.

Conventional PPI is a form of prodrug, which must be protonated to become an active form. To achieve this protonation process, the PPI should be reached in parietal cells in which acid secretion must be activated after the meal. Considering the time taken for this process, 30 minutes before the meal is required.[42] However, vonoprazan can be taken regardless of meal ingestion and the rate of absorption is not affected by meals.[15] The absorption speed of vonoprazan is rapid, and the time taken to reach maximum concentration in plasma is less than 2 hours after oral administration.[43] After absorption, the $T_{1/2}$ in plasma is approximately 2 hours for conventional PPIs, but up to 9 hours for vonoprazan.[44] Therefore, vonoprazan stays in the blood longer and can block acid secretion continuously.[45] The pharmacokinetics of vonoprazan are similar in Japanese and non-Japanese subjects.[45,46]

The CYP2C19 polymorphism influences the pharmacokinetics of conventional PPIs and affects interindividual variability in pharmacodynamics.[47] However, because vonoprazan is not primarily metabolized by CYP2C19,[44] the data from clinical studies on healthy volunteers and GERD patients showed limited influence by CYP2C19 polymorphisms.[35,45,46,48,49] Furthermore, the effects of clarithromycin, a potent CYP3A4 inhibitor, on the pharmacokinetics of vonoprazan were evaluated and no significant pharmacokinetic interactions were observed.[50]

Pharmacodynamics

Vonoprazan is effectively absorbed and quickly accumulates in parietal cells. In contrast, conventional PPIs require 3 to 5 days to achieve maximal and steady-state inhibition of acid secretion.[7,51] The effect is more pronounced after the first dose of vonoprazan compared to conventional PPIs; a single dose of 20 mg vonoprazan can increase intragastric pH to nearly 7 in as little as 4 hours.[46] This rapid onset of action is appropriate for the treatment of breakthrough GERD symptoms and for on-demand therapy. Furthermore, % time 24-hour intragastric pH above 4 of vonoprazan 20 mg once daily for 4 days and 7 days was 82.9% and 85.2%, respectively[46] and the effect continues without intragastric pH dipping below 4. The means of night-time pH above 4 after administration of vonoprazan 20 mg on day 1 were higher than after administration of esomeprazole 20 mg or rabeprazole 10 mg (Table 1).[48] Once this pH is maintained through daily administration, the pepsin produced by chief cells cannot be activated. Therefore, vonoprazan is a strong acid blocker that has rapid, stable, and long-lasting effects[35,46,48,52] and these effects were stronger than conventional PPIs[35,41,45,48,52,53] and prototype P-CAB.[41] Phase I studies of single ascending[45] and multiple repeat doses[46] in Japan and the United Kingdom revealed that vonoprazan was well-tolerated at single doses of 1-120 mg and at repeat doses of 10-40 mg.[54] The mean percentage of time that patients had a intragastric pH above 4 after multiple doses of 40 mg vonoprazan was 85.3% and 100.0% during the day and 86.5% and 100.0% at night (21:00-9:00) on days 1 and 7, respectively.[46]

Clinical Indications

Helicobacter pylori Eradication Therapy

H. pylori infection can be eradicated by elevating intragastric pH using an acid suppressant in combination with at least 2 antibiotics. *H. pylori* enters the growth phase from a stationary phase at intragastric pH above 5, at which point it becomes susceptible to antibiotics.[55,56] Although conventional PPIs have been used to suppress gastric acid secretion, recent *H. pylori* eradication rates have decreased due to increases in antibiotic-resistant *H. pylori* strains.[57] Increasing the dosage of PPIs and changing antibiotics have been attempted to increase the eradication rate.[58] In addition, the development of P-CABs that can strongly suppress acid secretion has been an attractive option for increasing the eradication rate. A randomized, double-blind study was conducted to prove the non-inferiority of 20 mg vonoprazan compared to 30 mg lansoprazole for the first-line triple therapy for *H. pylori* eradication with 750 mg amoxicillin and 200 mg or 400 mg clarithromycin.[59] Patients who did not achieve eradication also received second-line vonoprazan-based triple therapy with 750 mg amoxicillin and 250 mg metronidazole.[59] All drugs were administered orally twice daily for 7 days. The eradication rate with vonoprazan was 92.6% compared to 75.9% with lansoprazole.[59] Both first-line and second-line therapies were satisfactory and non-inferiority was proven.[59] A recent meta-analysis also showed the superiority of vonoprazan-based triple therapy compared to conventional PPI-based triple therapy.[60] Therefore, vonoprazan-based triple therapy should be the first-line treatment for *H. pylori* eradication (Table 1).[61]

Both prospective and retrospective studies have shown that the *H. pylori* eradication rate with vonoprazan-based triple therapy for clarithromycin-resistant subgroup was significantly higher than that with PPI-based triple therapy. Two prospective randomized controlled studies showed no difference in the eradication rate between vonoprazan-based and PPI-based triple therapies in clarithromycin-sensitive subgroup (Fig. 3).[59,62] However, two retrospective studies indicated a superior eradication rate with vonoprazan-based triple therapy.[63,64] These data indicate that the increased eradication rate with vonoprazan-based therapy is mainly gained in clarithromycin-

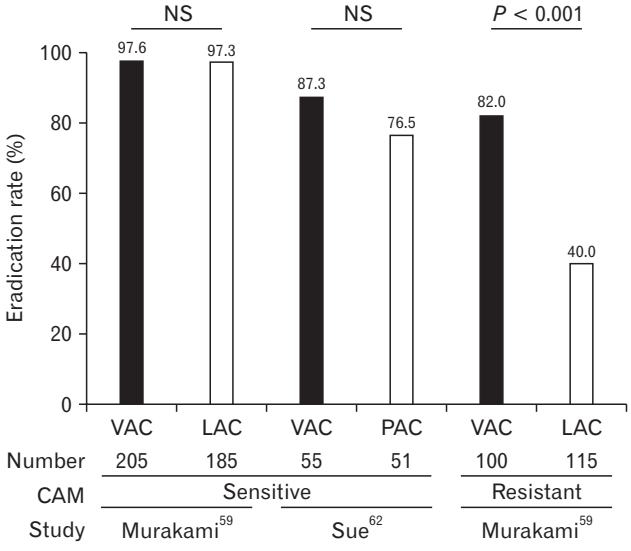

Figure 3. Eradication rate of *Helicobacter pylori* with vonoprazan and proton pump inhibitor (PPI). The *H. pylori* eradication rates by first-line triple therapies from randomized controlled trials are separately shown in clarithromycin (CAM)-sensitive and CAM-resistant subgroups. NS, not significant; VAC, vonoprazan + amoxicillin + clarithromycin; LAC, lansoprazole + amoxicillin + clarithromycin; PAC; PPI (lansoprazole, rabeprazole, or esomeprazole) + amoxicillin + clarithromycin.

resistant patients; thus, vonoprazan-based therapy must be effective for the clarithromycin-resistant *H. pylori* eradication, though sensitivity assay of clarithromycin of *H. pylori* is not recommended and is not included for reimbursement by Japan's national health insurance system.[65] Alternatively, when acid secretion can be effectively and strongly suppressed by vonoprazan, clarithromycin may not be needed for *H. pylori* eradication therapy. The dual therapy of amoxicillin and high-dose PPI or poor metabolizer of CYP2C19 that can maintain the intragastric pH above 6 leads to a high *H. pylori* eradication rate, because increasing the pH to 6 or 7 allows the bacteria to enter the replicative state where they become susceptible to amoxicillin.[57,66,67] Strong acid suppressive effect from the first dosage and even at night by vonoprazan may lead to a high *H. pylori* eradication rate. To prove this theory, a clinical study is ongoing in Japan (UMIN000022963).[68]

The eradication rate with vonoprazan-based triple therapy was also better than PPI-based triple therapy in young and middle age groups, indicating that strong acid inhibition is more effective in young than in old patients who may have less acid secretion with severe atrophic changes in gastric mucosa.[69] The effects of vonoprazan for the second-line treatment of *H. pylori* eradication are not well known. A meta-analysis of second-line triple therapy did not show a difference between vonoprazan and conventional PPIs.[60] As these data were obtained from retrospective studies, confounding factors might have existed that affected these results. In a single arm vonoprazan-based second-line triple therapy with amoxicillin and metronidazole in patients who failed vonoprazan- and lansoprazole-based first-line triple therapy, the eradication rate was as high as 98%.[59] Furthermore, vonoprazan-based triple therapies with amoxicillin and clarithromycin or with amoxicillin and metronidazole were safe and well-tolerated.[70-72] Another study showed that vonoprazan-based first-line therapy with amoxicillin and clarithromycin was effective in 70.2% of patients who failed rabeprazole first-line triple therapy with amoxicillin and clarithromycin in Japan.[73] There was even a case successfully treated with fourth-line vonoprazan-based triple therapy with amoxicillin and clarithromycin.[74] These data indicate that the fast onset of increase and sustained increase in intragastric pH are important factors for increasing the *H. pylori* eradication rate. In addition, the eradication rate was higher in subjects without NAB than in those with NAB.[75] Although there are few drug interactions, it should also be noted that vonoprazan treatment significantly decreased the value of the urea breath test (UBT).[76] Therefore, when UBT is performed to examine *H. pylori* eradication, vonoprazan treatment should be stopped at least 2 weeks before the test. Although the mechanisms how vonoprazan decreases the value of UBT are not clear, previous data have shown that urease activity is strongly affected by intragastric pH, particularly pH levels above 4-5.5.[77,78] Therefore, a rapid increase in intragastric pH in response to the early and strong acid inhibitory effect of vonoprazan may reduce urease activity.[45,46]

Gastroesophageal Reflux Disease

GERD is one of the most common esophageal diseases, characterized by symptoms of heartburn and acid regurgitation due to reflux of the stomach contents. The prevalence of GERD diagnosed by heartburn and/or acid regurgitation symptoms in East Asia is 2.5-7.8%.[79,80] The impact of GERD on quality of life (QOL) is large, and GERD is a burden on healthcare systems.[81,82] The major goals of treating erosive esophagitis are to relieve symptoms, heal erosions, and prevent complications.[83] Although host factors might exist because not all patients have abnormal gastroesophageal reflux, gastric acid is the principle factor underlying the development of reflux esophagitis, and PPIs have been the gold standard for treatment in the clinical setting.[3,84,85] Intragastric pH above 4 holding time has been used to show the effects of acid-suppressive drugs, because erosive esophagitis can be controlled and healed when this time is long.[86] However, the degree of acid suppression by PPIs

is not complete and no data have shown that a pH of 4 is enough to control reflux symptoms. Furthermore, approximately 80% of patients with frequent heartburn experience heartburn at night, and 29% of those are awakened by coughing or choking due to gastroesophageal reflux at night.[87,88] Nighttime acid reflux with NAB influences sleep quality and daytime QOL. More than 30% of patients on PPIs due to reflux esophagitis with heartburn continuously experience nocturnal heartburn;[89] therefore, this issue is one of the unmet clinical needs. More than 50% of symptomatic GERD patients taking PPIs are not satisfied with the treatment, and more than 20% of patients take PPIs twice daily or purchase medicines over the counter in addition to their prescribed medicine.[90]

The safety and dose–response profiles of vonoprazan were evaluated in an 8-week phase II study. Patients with erosive esophagitis were treated at doses of 5, 10, 20, and 40 mg once daily for 8 weeks and compared to those who were treated with 30 mg lansoprazole once daily for 8 weeks. Vonoprazan was effective and noninferior to lansoprazole for curing erosive esophagitis.[49] Although the study was designed to show the noninferiority of vonoprazan to lansoprazole, the healing rate of severe esophagitis (Los Angeles [LA] classification, Grades C/D) with 20 mg vonoprazan was higher than that with 30 mg lansoprazole at week 2 (96.0% vs 82.6%) (Fig. 4). In another phase II study, the noninferiority of 20 mg vonoprazan compared to 30 mg lansoprazole for treating erosive esophagitis was confirmed and the long-term efficacy of vonoprazan was evaluated.[91] In post hoc analyses, patients with severe esophagitis (LA Grades C/D) or with extensive CYP2C19 metabolism experienced better treatment effects in the vonoprazan group than in the lansoprazole group (Table 1). Long-term (52 weeks) maintenance treatment of 10 mg or 20 mg vonoprazan resulted in less than 10% erosive esophagitis recurrence and vonoprazan was well-tolerated overall. Vonoprazan was also assessed for the treatment of refractory GERD compared to conventional PPI. In an open label study, vonoprazan was effective for the treatment of PPI (standard single-dose)-refractory symptomatic GERD (Table 1).[92] Because this was an open label study, potential bias may have existed. However, the symptoms were quickly relieved in the study, and this effect might have correlated with the potent inhibition of acid production from the first dose of vonoprazan. Doses of 20 mg and 40 mg vonoprazan significantly inhibited gastric acid secretion after 24 hours and treated erosive esophagitis that was resistant to standard dose of conventional PPIs (Table 1).[93] Further studies are warranted to prove the rapid relief of GERD symptoms by vonoprazan.

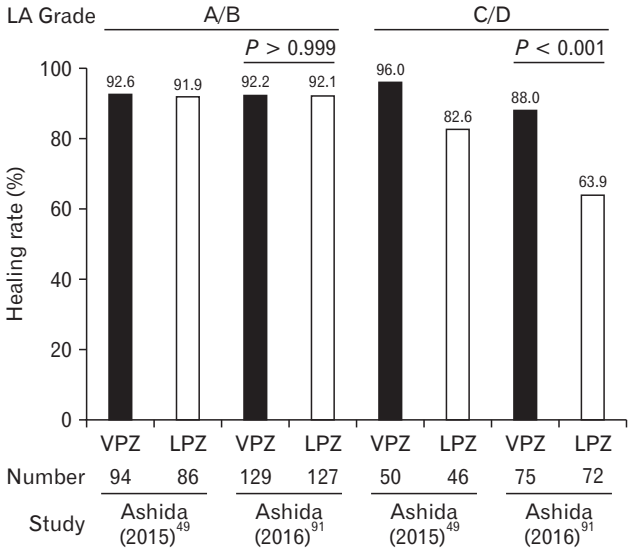

Figure 4. Healing rate of erosive esophagitis with vonoprazan (VPZ) and lansoprazole (LPZ) at week 2. Healing rates of erosive esophagitis with 20 mg VPZ and 30 mg LPZ at week 2 are separately shown in Los Angeles (LA) classification Grade A/B and C/D subgroups.

Treatment of Gastric and Duodenal Ulcers

Randomized, controlled trials confirmed the noninferiority of vonoprazan for the 8-week treatment of gastric ulcer (93.5% and 93.8% for vonoprazan and lansoprazole, respectively).[94] However, the noninferiority of vonoprazan compared to lansoprazole for the 6-week treatment of duodenal ulcer was not confirmed in the trial (95.5% and 98.3% for vonoprazan and lansoprazole, respectively). The factors that affected these data might have correlated with dropout subjects who did not complete the study and were counted as non-healed subjects. Some of the subjects might have stopped the study because their symptoms were quickly relieved by vonoprazan or lansoprazole. Further studies are needed to conclude the efficacy of vonoprazan for the treatment of gastric and duodenal ulcers.

Prevention of Recurrence of Low-dose Aspirin/Non-steroidal Anti-inflammatory Drug-related Ulcers

NSAIDs cause gastrointestinal (GI) ulcers and increase the risk of serious GI complications.[95] Risk factors associated with the occurrence of NSAID-related ulcers are history of GI ulcer with bleeding, concomitant use of two or more NSAIDs/low-dose aspirin (LDA), high dose of NSAIDs, concomitant use of anticoagulant agent, history of gastric and duodenal ulcers, age over 70 years, and *H. pylori* infection.[96-98] NSAID use and *H. pylori* infection are independent and synergistic risk factors for gastric and duodenal ulcers and bleeding.[99] This is the most important point

when considering NSAID-related gastric and duodenal ulcer and complications. Furthermore, not only NSAID and *H. pylori* infection but also host factors are involved in the development of ulcers. However, it is still not clear what definitive host factors are involved in the development of ulcers in *H. pylori*-infected patients and/or NSAID users. Therefore, patients at risk should discontinue NSAID use. However, this is sometimes not easy or feasible, as the continuous use of NSAIDs can control pain and improve QOL in patients with chronic pain.[100,101] LDA can also decrease the recurrence of cardiovascular and cerebrovascular diseases. In these cases, concomitant use of gastroprotective agents including PPI should be considered.[95]

A meta-analysis showed that PPIs significantly reduced the risk of NSAID-associated ulcers compared to placebo, and NSAIDs plus PPI was the most cost-effective strategy for preventing upper GI ulcers in patients on long-term NSAID therapy.[102] A dose of 20 mg esomeprazole once daily was effective and safe for preventing NSAID-associated upper GI ulcer recurrence.[103] Because NSAID-associated upper GI injury is pH-dependent, the higher the intragastric pH, the lower the incidence of injury.[104,105] Vonoprazan strongly inhibits acid production from the first dose. No clinically meaningful interactions during concomitant use of vonoprazan and NSAIDs were observed, and vonoprazan was well-tolerated when administered with LDA or NSAIDs.[106] Therefore, the efficacy and safety of vonoprazan for preventing NSAID-associated upper GI ulcer recurrence has been evaluated in patients continuously receiving NSAIDs in double-blind, randomized trials.[107] Vonoprazan (10 mg and 20 mg) was effective for NSAID-associated upper GI secondary ulcer prevention. These results were consistent with previous studies that investigated the effect of PPIs in NSAID-associated secondary ulcer prevention.[103,108,109] No unexpected adverse events were identified during at least a 1-year period of exposure to vonoprazan. After these data were introduced, the Japanese government approved 10 mg vonoprazan for the prevention of recurrent upper GI ulcers during long-term NSAID therapy.

The efficacy and safety of vonoprazan for preventing recurrent upper GI ulcer in patients with long-term LDA therapy was evaluated in a phase III study.[110] The rate of gastric and duodenal ulcer recurrence after 24 weeks of LDA therapy was 2.8%, and was 0.5% with 15 mg lansoprazole or 10 mg vonoprazan. Thus, 10 mg vonoprazan is as effective as 15 mg lansoprazole for preventing recurrent upper GI ulcer during LDA therapy.[110] Vonoprazan treatment resulted in lower ulcer recurrence rates and upper GI bleeding compared to lansoprazole during long-term LDA treatment. Vonoprazan has long-term safety (at least 24 weeks) and is well-tolerated.

Possible Complications of Potassium-competitive Acid Blockers

The more acid that is secreted, the more that effective acid suppression is needed, and the more the effects of vonoprazan stand out. When vonoprazan is used for short-term acid suppression, there are no problematic side effects. However, when long-term acid suppression treatment is needed, side effects such as hypergastrinemia, pneumonia, small bowel bacterial overgrowth, and *Clostridium difficile* infection may occur.[111-115] In clinical trials evaluating the safety and tolerability of vonoprazan for GERD[91] and LDA/NSAID-associated upper GI secondary ulcer prevention,[107,110] the common treatment-emergent adverse events (TEAEs) irrespective of causal relationship to study medication with an incidence of ≥ 5% in vonoprazan 10 mg and 20 mg were nasopharyngitis, diarrhea, constipation, upper respiratory tract inflammation, fall, gastroenteritis, and eczema. Most TEAEs were classified as mild in intensity. To verify the long-term safety and efficacy of vonoprazan, a study evaluating the safety of 5-year maintenance therapy of 10 mg or 20 mg vonoprazan in patients with healed erosive esophagitis is ongoing in Japan (NCT02679508).[116]

Conclusions

In conclusion, vonoprazan is superior to conventional PPIs for suppressing acid secretion, especially at night, and there was no difference in efficacy depending on CYP2C19 genotype status. In addition, vonoprazan was shown to overcome the weaknesses associated with conventional PPIs. The advantages of vonoprazan compared to previous P-CABs are that it does not have the hepatic toxicity observed with previous P-CABs, and it has slow dissociation from H^+, K^+-ATPase while its actions are long-lasting. In clinical trials, vonoprazan showed potent acid-suppressive effects, and rapid and long-lasting effects for the treatment of acid-related diseases including reflux esophagitis, LDA/NSAID-associated ulcer recurrence, and *H. pylori* infection. It also had satisfactory safety and tolerability after at least 1 year of treatment. Thus, vonoprazan may address the unmet medical need for the treatment of acid-related diseases.

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