ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

Insights on the Potential Use of Potassium-Competitive Acid Blockers in Erosive Esophagitis

Colin W. Howden, MD
Hyman Professor of Medicine
Chief, Division of Gastroenterology
University of Tennessee Health Science Center
Memphis, Tennessee

G&H How do potassium-competitive acid blockers compare with traditional proton pump inhibitors in terms of mechanism of action?

CH Potassium-competitive acid blockers (P-CABs) inhibit the proton pump but at a different site and through a different mechanism of action than proton pump inhibitors (PPIs). P-CABs interact with the potassium channel adjacent to the proton pump. They bind ionically, unlike PPIs, which bind covalently. This means that the binding action of P-CABs is potentially reversible. These agents have a faster onset of action than PPIs, and they have a more sustained action in inhibiting acid secretion.

G&H How effective are PPIs in the treatment of erosive esophagitis? Why is there a need to pursue alternative therapies?

CH Generally, PPI treatment is effective for erosive esophagitis; however, not all patients achieve complete mucosal healing with a standard 8-week course of a PPI. This is especially true for patients with severe erosive esophagitis—that is, those with Los Angeles grades C and D erosive esophagitis. The efficacy of PPI treatment is dependent, to some extent, on an individual's cytochrome P450 2C19 (*CYP2C19*) genotype. Those who are genetically determined, rapid metabolizers may have reduced efficacy of PPI treatment. This is not the case for P-CABs, which are not metabolized via *CYP2C19*. However, perhaps the greatest potential advantage of a P-CAB over a PPI in erosive esophagitis relates to maintenance treatment.

G&H What research has been conducted comparing P-CABs with PPIs for the treatment of erosive esophagitis?

CH P-CABs have not yet been approved for use in the United States. Data from clinical trials conducted in Asia—predominantly in Japan—demonstrate that P-CABs are effective treatments for erosive esophagitis. They have been shown to be noninferior to PPIs. A recent phase 3 clinical trial by Xiao and colleagues that compared the investigational P-CAB vonoprazan with the PPI lansoprazole in 468 patients with erosive esophagitis found healing rates of 85% for both treatments at 4 weeks and healing rates of 75% and 68% for vonoprazan and lansoprazole, respectively, at 8 weeks. Rates of treatment-associated adverse effects were 38% and

37% for vonoprazan and lansoprazole, respectively. The researchers concluded that vonoprazan was noninferior to lansoprazole.

However, P-CABs may be superior to PPIs in terms of the speed of healing of erosive esophagitis and in healing severe grades of esophagitis. In addition, P-CABs have shown lower relapse rates compared with PPI treatment in the maintenance of healing of erosive esophagitis. A study by Ashida and colleagues of 409 patients randomized to either vonoprazan or lansoprazole is among a handful of recent studies that have confirmed noninferiority. Whether patients were grouped according to age, sex, Los Angeles classification grade, *Helicobacter pylori* status, or *CYP2C19* genotype, the proportion of patients who achieved healing at week 8 with vonoprazan was generally equal to or higher than that with lansoprazole. This study also followed 305 patients who were maintained on vonoprazan for 52 weeks. The recurrence rate was less than 10%.

> … maintenance treatment with vonoprazan was significantly superior to maintenance treatment with lansoprazole for keeping erosive esophagitis healed over the course of 6 months.

Only small, uncontrolled studies have examined P-CAB treatment for patients whose erosive esophagitis had been unresponsive to PPI treatment. In one open-label study, vonoprazan healed PPI-refractory erosive esophagitis in 8 of 12 patients.

G&H What insights from these clinical trial results are particularly pertinent to gastroenterologists in clinical practice?

CH As previously mentioned, in general, P-CABs are at least noninferior to PPIs in healing all grades of erosive esophagitis. The aforementioned study by Ashida and colleagues showed more rapid healing of erosive esophagitis in patients on a P-CAB than in those on a PPI and higher healing rates for patients with Los Angeles grades C and D erosive esophagitis. At least one small study suggests that a P-CAB was superior to a PPI in terms of speed of symptom relief in patients with erosive esophagitis. Likely the most important finding from a clinical trial in Japan, also conducted by Ashida and colleagues, is that maintenance treatment with vonoprazan was significantly superior to maintenance treatment with lansoprazole for keeping erosive esophagitis healed over the course of 6 months. In this study, 607 patients with healed erosive esophagitis following 8 weeks of vonoprazan 20 mg/day were randomized to receive lansoprazole 15 mg/day, vonoprazan 10 mg/day, or vonoprazan 20 mg/day for 24 weeks. Recurrence rates within the 24-week period were 17% with lansoprazole 15 mg/day, 5% with vonoprazan 10 mg/day, and 2% with vonoprazan 20 mg/day.

G&H What is known about the safety profiles of P-CABs in comparison with the safety profiles of the PPIs that are currently available?

CH At the moment, the safety profiles of the P-CABs that are currently in use elsewhere in the world are being studied closely. Thus far, findings have been very positive. No unexpected safety signals have arisen.

As for PPIs, it is important to note that they have excellent overall safety profiles. There have been multiple recent studies raising various safety concerns with PPIs, but almost all of these studies have been retrospective in nature, prone to confounding bias, and of insufficient strength to establish any causal relationships.

It should also be noted that serum gastrin levels increase during treatment with a P-CAB just as they do during treatment with a PPI, although the elevation may be slightly higher with P-CABs. However, thus far, this has not led to any safety issues, and I do not expect that it will be associated with any going forward. Ongoing safety monitoring studies will include measurement of serum gastrin levels and histopathologic studies on the gastric mucosa in patients on long-term P-CAB treatment.

G&H Which P-CABs are currently in late-stage development worldwide and specifically in the United States?

CH As of February 2021, tegoprazan, revaprazan, and fexuprazan are available in South Korea. Revaprazan is also approved in India. Vonoprazan is currently approved in 14 countries or territories in Asia and South America. There are few head-to-head comparisons of different P-CABs; however, a study recently published in *Alimentary Pharmacology and Therapeutics* compared the

pharmacodynamics of approved doses of tegoprazan and revaprazan in South Korea. Tegoprazan 50 mg once daily controlled 24-hour intragastric acidity for significantly longer than revaprazan 200 mg once daily.

If vonoprazan is approved, it would be the first antisecretory agent from a new class of drugs (ie, P-CABs) to be approved in the United States in more than 30 years.

To the best of my knowledge, vonoprazan is the only P-CAB that is currently in phase 3 clinical trials in the United States. There are ongoing clinical trials with vonoprazan for the treatment of erosive esophagitis as well as the treatment for *H pylori* infection. The results of those trials should be available later in 2021.

If vonoprazan is approved, it would be the first antisecretory agent from a new class of drugs (ie, P-CABs) to be approved in the United States in more than 30 years. It received fast-track status by the US Food and Drug Administration for the treatment of *H pylori* infection in 2019.

G&H What are the next steps in research?

CH As noted, vonoprazan is currently being evaluated in the United States as well as in Europe for the potential indications of healing, and maintenance of healing, of erosive esophagitis. In combination with 1 or 2 antibiotics, it is also being evaluated for the treatment of *H pylori* infection. The sponsor of those trials is also planning to conduct research on vonoprazan for the treatment of nonerosive reflux disease.

Disclosures

Dr Howden is a consultant for Phathom Pharmaceuticals, RedHill Biopharma, Clexio, Ironwood, and ISOThrive. He is a speaker for RedHill Biopharma, Alnylam, and Alfasigma. He owns stock in Antibe Therapeutics.

Suggested Reading

Ashida K, Iwakiri K, Hiramatsu N, et al. Maintenance for healed erosive esophagitis: phase III comparison of vonoprazan with lansoprazole. *World J Gastroenterol.* 2018;24(14):1550-1561.

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(2):240-251.

Iwakiri K, Sakurai Y, Shiino M, et al. A randomized, double-blind study to evaluate the acid-inhibitory effect of vonoprazan (20 mg and 40 mg) in patients with proton-pump inhibitor-resistant erosive esophagitis. *Therap Adv Gastroenterol.* 2017;10(6):439-451.

Miyazaki H, Igarashi A, Takeuchi T, et al. Vonoprazan versus proton-pump inhibitors for healing gastroesophageal reflux disease: a systematic review. *J Gastroenterol Hepatol.* 2019;34(8):1316-1328.

Sunwoo J, Ji SC, Oh J, et al. Pharmacodynamics of tegoprazan and revaprazan after single and multiple oral doses in healthy subjects. *Aliment Pharmacol Ther.* 2020;52(11-12):1640-1647.

Xiao Y, Zhang S, Dai N, et al. Phase III, randomised, double-blind, multicentre study to evaluate the efficacy and safety of vonoprazan compared with lansoprazole in Asian patients with erosive oesophagitis. *Gut.* 2020;69(2):224-230.