EVIDENCE-BASED GI
AN ACG PUBLICATION

Vonoprazan is Efficacious for Non-Erosive Reflux Disease (NERD): An Alternative for PPI-Resistant NERD Patients?

Christopher Vélez, MD

Associate Program Director, Advanced Fellowship in Functional and Gastrointestinal Motility Disorders, Center for Neurointestinal Health, Division of Gastroenterology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Christopher Vélez, MD
Associate Editor

This summary reviews Laine L, Spechler S, Yadlapati R et al. Vonoprazan is efficacious for treatment of heartburn in non-erosive reflux disease: A randomized trial. Clin Gastroenterol Hepatol 2024; In Press. doi: 10.1016/j.cgh.2024.05.004.

Correspondence to Christopher Velez, MD. Associate Editor. Email: EBGI@gi.org

Keywords: vonoprazan, Gastro-esophageal Reflux Disease (GERD), Non-erosive Reflux Disease (NERD)

STRUCTURED ABSTRACT

Question: Is oral vonoprazan 10 mg daily or 20 mg daily (qd) effective in the management of non-erosive reflux disease (NERD)?

Design: Multicenter, double-blind, placebo-controlled randomized trial.

Setting: Ninety-one ambulatory sites throughout the United States.

Patients: Adult patients with a diagnosis of symptomatic gastroesophageal reflux disease (GERD) with heartburn as their predominant symptom with onset greater than 6 months, with heartburn at least 4 days during any consecutive 7-day period during screening and no esophagitis on upper endoscopy.

Key exclusion criteria included erosive esophagitis on endoscopy, *Helicobacter pylori* infection, antibiotic exposure within 4-weeks and use of other acid suppressing medications (histamine 2-receptor antagonists [H2Bs] and proton pump inhibitors [PPIs]) within 2-weeks. Presence of esophageal intestinal

metaplasia (Barrett's esophagus) would also result in exclusion.

Interventions/Exposure: Eligible subjects were randomly assigned with concealed allocation via a central randomization sequence generator. They were randomized in a 1:1:1 ratio in the 4-week placebo-controlled period to vonoprazan 10 mg, vonoprazan 20 mg, or placebo taken once-daily. During an 20-week extension period, those randomized to placebo initially were re-randomized in 1:1 fashion to either 10 mg or 20 mg dosing. Rescue antacid (Gelusil; Wellspring Consumer Healthcare, Sarasota, FL) was provided. After completing the 20-week extension period, an additional 4-week follow-up of selected subjects was performed.

Outcome: Subjects completed an electronic diary for heartburn and use of rescue antacids twice daily: every morning upon waking to record the previous night's maximum heartburn severity, and every night before bedtime to record that day's maximum heartburn severity. Heartburn severity was graded on a scale of 0 (no heartburn) to 4 (very severe heartburn).

The primary outcome was the percentage of days without daytime or nighttime heartburn (24-hour heartburn-free days) over the 4-week treatment period. Secondary outcomes included percentage of days without antacid rescue usage and mean severity of heartburn.

Data Analysis: Intention-to-treat (ITT) analysis was performed. Sample size was calculated assuming an efficacy of 50% for vonoprazan dosing in the percentage of days without daytime or nighttime heartburn over the 4-week placebo-controlled study (as well as to detect a 20% difference between vonoprazan and placebo dosing with a standard deviation of 35%). These targets were established in line with prior placebo-controlled studies in the United States for vonoprazan. This resulted in a suggested sample size of 250 individuals.

Funding: Phathom Pharmaceuticals (Buffalo Grove, IL), manufacturer of vonoprazan.

Results: Between February 2022 and October 2022, 776 subjects were randomized in the placebo-controlled phase, with 739 individuals completing this phase and 728 participants randomized into the extension phase. Non-compliance was broadly similar among each of the 3 arms (ranging from 3.1 to 4.7%). Vonoprazan 10 mg and vonoprazan 20 mg daily dosing increased the percentage of 24-hour symptom-free days in comparison to placebo (placebo: 27.7%; 10 mg: 44.8%; 20 mg: 44.4%). The effect was rapid, with approximately 10% of the difference between vonoprazan and placebo occurring with the administration of 1 dose, and

20% with the second dose. In those subjects followed over 6 months, this increase in symptom-free days persisted and gradually increased to 60%-70% of days. There was no difference in efficacy between 10 mg and 20 mg daily vonoprazan dosing. As expected physiologically, gastrin levels increased in recipients receiving vonoprazan.

COMMENTARY

Why Is This Important?

Gastroesophageal reflux disease (GERD) is a highly prevalent family of conditions ranging from functional heartburn to erosive esophagitis for which no significant pharmacologic therapy innovation has occurred since the 1980s until potassium competitive acid blockers (PCABs) like vonoprazan were approved. Pre-PCABs, prescribed therapy was limited to histamine 2-receptor antagonists (subject to tachyphylaxis) and proton pump inhibitors (subject to cumbersome pre-prandial dosing and taking the medication with regularity). Previous data has shown that PCABs significantly improve healing of erosive esophagitis compared to PPIs. By showing that vonoprazan also improves nonerosive reflux disease (NERD) symptoms, this study expands the populations potentially benefiting from PCAB therapy and led the FDA to approve vonoprazan 10 mg daily for NERD.

The American College of Gastroenterology's 2022 guidelines on the diagnosis and management of gastroesophageal reflux disease (GERD)[1] recommend an 8-week trial of empiric PPIs and to discontinuation of PPIs in patients whose classic GERD symptoms respond to an 8-week empiric trial of PPIs. Vonoprazan upends these guidelines as this administration recommendation can likely be shortened if PCABs are used increasingly in lieu of PPIs given how quickly patients can respond to PCABs. In addition, while 2022 guidelines recommend a conceptual rationale for a trial of switching PPIs to patients who have not responded to 1 PPI and that more than 1 switch to another PPI cannot be supported, it may become common to switch directly to a PCAB if 1 PPI taken correctly fails to control symptoms.

Additionally, the pharmacology of PCABs is more amenable to as-needed dosing. As opposed to PPIs, which are a pro-drug and need to be swallowed into an acidic empty stomach and then followed by eating food 30 minutes later to activate acid pumps, PCABs can be swallowed with or without food and do not require eating food 30 minutes after ingestion to turn on acid pumps and optimize efficacy. This could provide advantages for NERD patients given the lack of mucosal injury. In patients who do not wish to be burdened by pre-prandial timing or are concerned about daily PPI administration, it will likely be more difficult to convince them to do so in the vonoprazan era. As vonoprazan

acts via on-demand mechanisms compared to PPIs, gastroenterologists will have to update communication scripts and shared decision-making models for NERD management, which is not as clearcut as erosive esophagitis management.

Key Study Findings

Vonoprazan 10 mg and vonoprazan 20 mg daily dosing increased the percentage of 24-hour symptom-free days in comparison to placebo (placebo: 27.7%; 10 mg: 44.8%; 20 mg: 44.4%). The effect was rapid, with approximately 10% of the difference between vonoprazan and placebo occurring with the administration of 1 dose, and 20% with the second dose.

Caution

The major limitation is that patients were defined as having non-erosive reflux disease without ambulatory reflux monitoring, which would differentiate NERD symptoms due to an elevation in the acid exposure time and/or number of acidic reflux episodes versus other disorders. Thus, this NERD cohort included similar GERD-spectrum conditions like reflux hypersensitivity and functional heartburn which are more related to disordered gut-brain interaction (DGBI) and less to pathologic acid-related mucosal injury (which PCABs treat).

While the authors correctly state that switching to PCAB therapy without reflux testing would be closer to what is done in clinical practice, readers should not surmise that switching to vonoprazan is a panacea to refractory GERD symptoms. Ambulatory reflux monitoring should still be considered according to the Lyon 2.0 consensus[2], to identify reflux hypersensitivity and functional heartburn for whom other treatment modalities may be appropriate (including neuromodulators).

My Practice

Based on this RCT, in patients who are hesitant to undergo wireless or catheter-based ambulatory reflux testing, I would consider switching to vonoprazan with refractory NERD symptoms. This would be subject to prior authorization/formulary considerations. As management of reflux hypersensitivity and functional heartburn bear more similarity to DGBI-spectrum conditions, I recommend ambulatory testing in PPI refractory cases. However, I practice in a tertiary academic medical center with ready access to reflux monitoring which I can interpret personally; most practicing gastroenterologists do not have that luxury.

For Future Research

Future trials involving vonoprazan for NERD should study optimal parameters for recommending on-demand administration for NERD. In erosive esophagitis, due to mucosal injury, standing dosing is reasonable to heal or further prevent further erosive disease. Daily administration in NERD is of less clear necessity. In addition, the as-needed pharmacology of vonoprazan is attractive for patients who are hesitant to use a once- or twice-daily acid suppression regime such as those recommended for

PPIs (and has already been shown to be effective from a symptom perspective[3]). It would be helpful for such future PCAB studies to consider the use of ambulatory reflux monitoring to clarify why participants do not respond to PCABs when they suffer from NERD. If patients can be reliably identified as having functional heartburn or reflux hypersensitivity if they fail to respond to PCAB therapy, this would be a useful addition to the literature which could inform updated parameters for referral to ambulatory reflux monitoring.

Conflict of Interest

Dr. Vélez has received research funding from Ironwood Pharmaceuticals.

REFERENCES

1. Katz P, Dunbar KB, Schnoll-Sussman FH, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol 2022; 117(1):27-56.
2. Gyawali CP, Yadlapati R, Fass R, et al. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. Gut 2024; 5;73(2):361-371.
3. Fass R, Vaezi M, Sharma P, et al. Randomised clinical trial: Efficacy and safety of on-demand vonoprazan versus placebo for non-erosive reflux disease. Aliment Pharmacol Ther 2023;58(10):1016-1027.