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On-Demand Vonoprazan for Non-Erosive Reflux Disease Symptoms: A New Option

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This summary reviews 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 Nov;58(10):1016-1027 .

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STRUCTURED ABSTRACT

Question: Is oral vonoprazan 10 mg daily, 20 mg, or 40 mg daily effective "on-demand" in the management of non-erosive reflux disease (NERD)?

Design: Multicenter, blinded, placebo-controlled randomized trial.

Setting: Fifty-four ambulatory sites throughout the United States.

Patients: Adult patients with non-erosive reflux disease with negative endoscopies participated in this study. A negative endoscopy consisted of an absence of reflux-related changes. This included an absence of any grade of erosive esophagitis by the Los Angeles grading system, Barrett's esophageal intestinal metaplasia, or other mucosal abnormalities. The Rome IV classification scheme for disordered gut-brain interaction was used to diagnose patients with functional

heartburn and functional dyspepsia for exclusion; there was no ambulatory reflux monitoring to distinguish between NERD and functional heartburn. Additional exclusion included those with eosinophilic esophagitis, esophageal varices, esophageal stricture, infectious esophagitis, and history of caustic or radiation-related trauma to the esophagus.

Interventions/Exposure: During a 4-week open-label run-in period, all patients were administered vonoprazan 20 mg daily. Afterwards, eligible patients were randomized in 1:1:1:1 fashion to receive vonoprazan 10 mg, 20 mg, 40 mg, or placebo in the 6-week on-demand study period. During the study period, the study agent was taken at the onset of symptoms, with only one dose being eligible for a 24-hour period. Rescue antacid was provided during pre-screening through the on-demand period and for 1-week subsequently during a "safety follow-up" period.

Outcome: The primary outcome was the percentage of heartburn episodes that were completely relieved within 3-hours and without further symptoms for 24-hours after use of study drug, including lack of a need to take rescue antacid. Secondary outcomes included: (1) relief of symptoms within 3-hours, with possible recurrence within 24-hours; (2) the mean number of rescue antacid tablets taken per day; (3) the percent of days that the study drug was taken during the on-demand period; and, (4) the percentage of 24-hour symptom-free days during the on-demand period among other secondary endpoints.

Data Analysis: Intention-to-treat (ITT) analysis was performed. Sample size was calculated assuming that each patient would have 4 evaluable heartburn episodes and that there would be a difference of 15% between each vonoprazan dose and placebo for the primary endpoint. It was assumed that 50 patients (with at least 4 episodes) in each arm would be necessary. A high rate of ineligibility (due to a lack of heartburn episodes) of 60% was posited, resulting in the target of 500 patients needing to be recruited for the run-in period, to achieve 200 subjects (50 participants in each arm). Secondary end point analyses were performed using either Fisher's exact text or a rank-sum test.

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

Results: A total of 1,115 patients were screened for the study, with 458 subjects

enrolled into the run-in period. The cohort was primarily female(64.8%). The majority of screen failures occurred due to not having filled out enough diary entries as well as having had heartburn episodes within the last 7 days of the run-in period. A total of 207 patients were randomized into the 6-week on-demand period, with roughly equal allocation in each of the 4 study arms (all groups with either 51 or 52 participants).

In all 3 doses of vonoprazan (10 mg, 20 mg, and 40 mg), there were significantly more heartburn episodes relieved completely within 3-hours with sustained relief for 24-hours compared to placebo: vonoprazan 10 mg: 56.0%; vonoprazan 20 mg: 60.6%; vonoprazan 40 mg: 70.0%; placebo: 27.3%, $P<0.0001$ (Figure 1). A similar trend was elicited when examining solely for relief within 3-hours (a secondary end point).

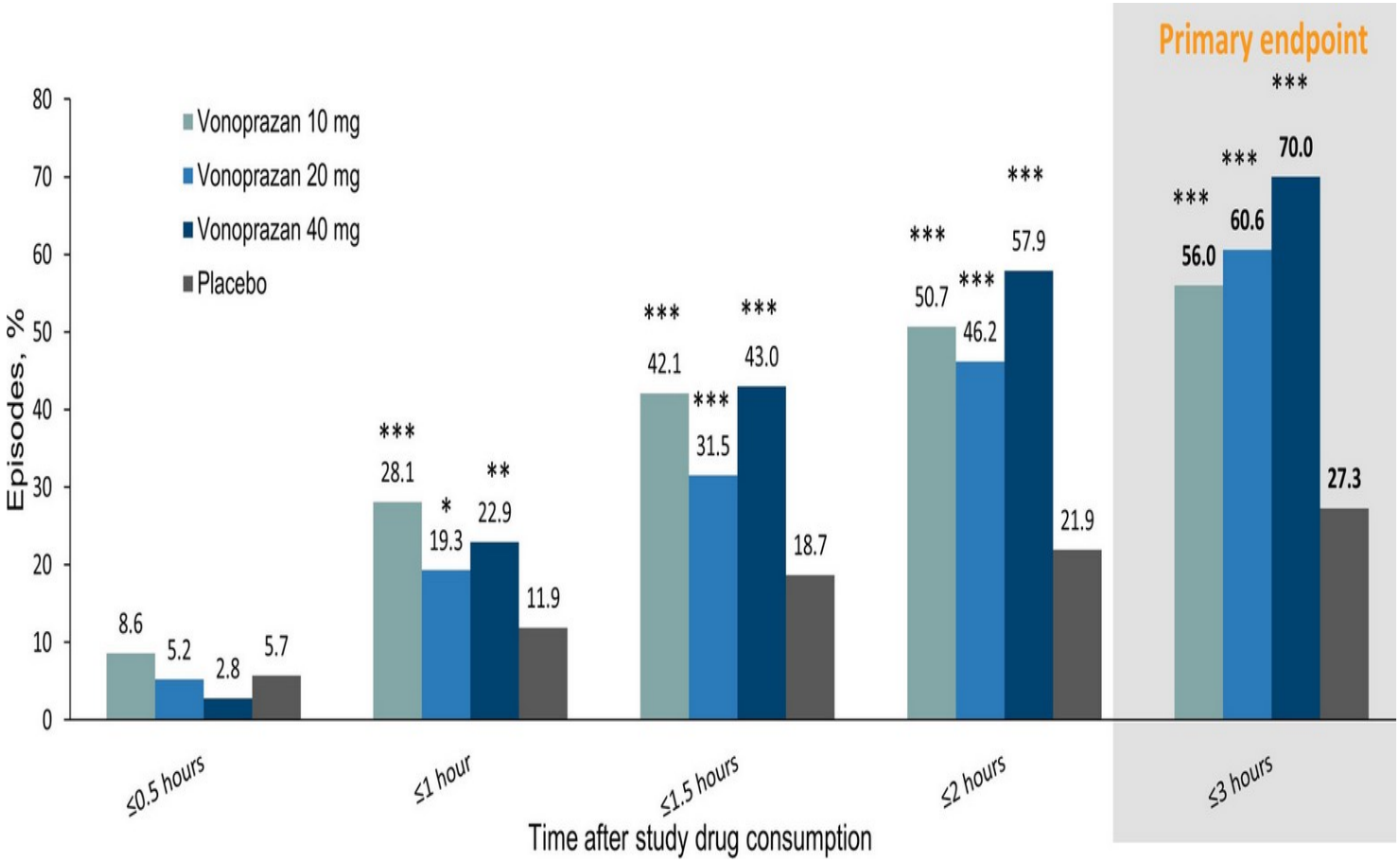

Figure 1. Proportion of heartburn episodes relieved within 3 hrs or less with no further heartburn symptoms in next 24 hours.

COMMENTARY

Why Is This Important?

The family of illnesses termed "gastroesophageal reflux disease" (GERD) includes a range of conditions from erosive esophagitis to non-erosive reflux disease (NERD) to reflux hypersensitivity and functional heartburn. The former 2 conditions are marked by acid-related changes to the esophagus, and the latter 2 disorders are thought to be more representative of a nerve hypersensitivity state, including potentially disordered gut-brain interaction. Recent literature is rich in describing the benefit of potassium competitive acid blockers (PCABs), like vonoprazan, for a variety of foregut conditions, especially since vonoprazan 20 mg has a more rapid onset of action (< 2 hours) and has a longer halflife than standard dose proton pump inhibitor (approximately 8 hours vs 1.5 hours, respectively) while also being approximately 100-fold more potent at acid suppression. Additionally, vonoprazan can be taken with or without food while proton pump inhibitors should be taken on an empty stomach and followed by eating food 30-60 minutes later for optimal efficacy. Therefore, this article expands that paradigm further—it queries for the benefit of on-demand vonoprazan usage for NERD. It demonstrates that such a benefit exists for PCABs.

Most recent acid suppression guidelines for the treatment of GERD- spectrum complaints center on the penultimately developed treatment class, proton pump inhibitors (PPIs). The American College of Gastroenterology's 2022 GERD guidelines[1] recommend an 8-week trial of empiric PPIs and to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-week empiric trial of PPIs. Vonoprazan adjusts the NERD treatment landscape. For patients who may be hesitant to pursue daily administration of PPIs, it will become increasingly untenable to "force" them to take a daily medication for NERD-spectrum complaints when PCABs exist that are potent suppressors that can be taken as needed.

Key Study Findings

Vonoprazan 10 mg, vonoprazan 20 mg, and vonoprazan 40 mg on-demand dosing was more effective than placebo at improving NERD symptoms within 3-hours of administration as well as within 1 hour or within 2 hours (**Figure 1**).

It resulted in an improvement that was sustained over 24-hours as well. This builds on literature associating PCAB utilization with effective *Helicobacter pylori* treatment, healing of erosive esophagitis, and daily management of NERD.

Caution

As with other studies looking at the use of PCABs to treat GERD-spectrum complaints, the major limitation of this article is the lack of ambulatory reflux monitoring, which is the only modality that differentiates reliably NERD from

reflux hypersensitivity and functional heartburn. While the authors preemptively address this by stating that current diagnostic criteria for NERD do not require such monitoring, it remains an unknown in this study. I question how the authors were able to address functional heartburn in particular, as this was a condition that was excluded from enrollment. Namely, functional heartburn criteria include the presence of "no" symptom relief of heartburn symptoms despite optimal use of acid suppressing therapy. In my clinical practice at least, rarely does someone describe a total lack of symptom relief from acid suppression therapy, but rather a less-than-expected benefit. I suspect that there are a large number of people represented in this study who actually have functional heartburn (possibly those not responding well to vonoprazan administration). This methodologic limitation most likely minimized the documented efficacy of vonoprazan since patients with functional heartburn usually have minimal response to acid suppression medications.

Additionally, there is a discrepancy with evidence-based consensus as to the importance of Los Angeles Grade A esophagitis. The Los Angeles grading scheme has been well accepted for over 20 years[2]. In this study, LA Grade A patients were excluded; Lyon 2.0 consensus generally minimizes the importance of LA Grade A esophagitis in clinical decision making. Namely, Lyon considers only LA Grade B, C, or D esophagitis as evidence of acid-related damage secondary to GERD[3]. In view of the increased role of the Lyon protocol in the management of GERD, it could have been useful to include participants in this study with LA Grade A esophagitis as this would reflect more accurately clinical practice as it relates to reflux esophagitis severity.

My Practice

Based on this trial, I find that my hesitancy towards using vonoprazan centers on the bane of clinicians' existence: cost, formularies, and prior authorization. There is the potential for inequity as well in the use of vonoprazan, as those capable of out-of-pocket payment or with excellent coverage via commercial insurance may more frequently obtain PCAB prescription. That being said, I think the success of vonoprazan has changed permanently the GERD/NERD treatment landscape. With patients at times concerned with the consequences of frequent PPI usage, it will become increasingly untenable to recommend they take a daily medication in the absence of erosive esophagitis if on-demand PCABs are sufficient to control their symptoms. As a neuromotilist, I am prepared for vigorous debate in the foregut disease world, centered on use of the first new class of acid suppressing therapy since omeprazole was approved in the late 1980s.

For Future Research

The yawning gap that has existed in research studies of vonoprazan is the lack of ambulatory reflux monitoring to fur-

ther characterize research cohorts. Generally, study authors have correctly stated that the absence of reflux monitoring reflects normal clinical practice, where access to such technology is uneven. Yet, ambulatory reflux monitoring remains the gold standard that should be employed as it relates to defining the physiologic necessity for acid suppression. Clinically, it still benefits patients long term to receive reflux hypersensitivity or functional heartburn diagnoses (thus avoiding unnecessary pharmacologic treatment). Accurately defining who would benefit from PCABs can best occur through ambulatory reflux monitoring – this is the next best step for vonoprazan-related research.

Conflict of Interest

Dr. Vélez reports no potential conflict of interest.

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