ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Potassium-Competitive Acid Blockers and Gastroesophageal Reflux Disease

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G&H How do potassium-competitive acid blockers differ from proton pump inhibitors?

DA Proton pump inhibitors (PPIs) are prodrugs that are not active as absorbed but are activated in the presence of acid. PPIs are taken up by parietal cells where, in the acidic secretory canaliculi, they are irreversibly converted to a sulfenamide form which is trapped in the canaliculus. The sulfenamide then binds covalently and irreversibly with the hydrogen potassium adenosine triphosphatase (H+/K+ ATPase), or proton pump, to block the hydrogen ion secretion channel; however, PPIs act on proton pumps that are actively secreting acid. Potassium-competitive acid blockers (P-CABs), on the other hand, are active when absorbed. Although they, too, accumulate in parietal cell secretory canaliculi, they act by blocking the potassium channel of the proton pump, through reversible, ionic binding of both active and inactive proton pumps.

P-CABs and PPIs both act on the proton pump but, because they achieve their effects by different means, they have different pharmacokinetic and pharmacodynamic properties. PPI levels peak at about 90 to 120 minutes, whereas P-CABs peak at about 8 or 9 hours after ingestion. P-CABs achieve peak acid suppression more rapidly because their effect is not limited to active proton pumps, and they have a longer intrinsic duration of effect because they remain in the bloodstream for a longer period of time. These differences with respect to speed of onset, duration of action, and mechanism might, then, allow for the possibility of personalized treatment to meet individual needs. However, although there is an opportunity for personalization, therein lies the rub, which is our current inability to identify accurately those individuals who would benefit from a P-CAB rather than a PPI.

G&H Which P-CABs have shown promise in the treatment of acid-related diseases?

DA P-CABs have actually been around for a long time, and data show that they are effective. That is, P-CABs have shown promise for treating acid-related diseases, but the real question is whether they promise to be more effective than PPIs. Of the P-CAB class, vonoprazan (Takecab, Takeda) is probably the best known and has been available for the treatment of acid-related diseases in Japan since 2015. Tegoprazan (K-Cab, HK inno.N/RaQualia Pharma) was approved for use in South Korea in 2019. Studies are evaluating fexuprazan, keverprazan, and revaprazan. Two other P-CABs, linaprazan glurate and zastaprazan, are in development. In fact, the results of an earlier randomized comparative study had shown that AZD0865 (from which the prodrug linaprazan glurate was developed) was effective but not better than esomeprazole in patients with esophagitis.

In the United States, vonoprazan has been evaluated in large clinical trials for the treatment of patients with gastroesophageal reflux disease (GERD) and erosive esophagitis (EE). A very recent randomized controlled trial in the United States and Europe reported that vonoprazan was noninferior, overall, to lansoprazole for healing and maintenance of EE and, importantly, that vonoprazan was superior to lansoprazole for healing and maintenance

of severe (Los Angeles Classification [LA] grade C or D) EE. In addition, a recently published randomized controlled phase 3 trial reported that vonoprazan-based regimens were superior to PPI-based triple therapy for *Helicobacter pylori* eradication and there are some early studies evaluating vonoprazan as a proof of concept with on-demand therapy for long-term maintenance in nonerosive reflux disease (NERD). Two vonoprazan-containing *H pylori* treatment regimens (vonoprazan plus amoxicillin and clarithromycin [Voquezna Triple Pak, Phathom] and vonoprazan plus amoxicillin [Voquezna Dual Pak, Phathom]) have been approved by the US Food and Drug Administration, and a New Drug Application for vonoprazan for the treatment of EE has been accepted. In summary, P-CABs have shown promise in relation to PPIs, consistent with the pH studies, which show that they may have more rapid onset and a longer duration of action. Like the PPIs and H2 blockers, it is likely that P-CABs have an overall class effect, but they are probably not all identical and individual P-CABs may differ depending on their pharmacologic properties.

In the short term, data suggest that there is no significant difference between P-CABs and PPIs.

G&H What has research shown so far on P-CAB use in the treatment of EE and NERD?

DA I think research has shown that P-CABs are effective, and they are at least as effective in the comparable studies. For instance, the P-CAB AZD0865 was found to be comparable in efficacy to esomeprazole, both for EE and for NERD. As I said, the trouble was that AZD0865 was not better than the PPI. Subsequent studies with vonoprazan suggest that—at least in the doses they chose to compare P-CABs with PPIs—vonoprazan may produce healing in a greater proportion of patients with more severe esophagitis (LA grade C/D). The healing rate was 8.3% greater for vonoprazan 20 mg than for lansoprazole 30 mg in all patients with EE and 19.6% greater for patients with more severe disease (LA grade C/D); healing maintenance rates at 24 weeks were 7.2% higher for all patients with EE and 13.3% higher for patients with severe EE receiving vonoprazan 10 mg compared with patients receiving lansoprazole 15 mg daily.

For NERD, the picture is less clear. Part of the problem, even in clinical studies, is that NERD is a heterogeneous condition; one is treating patients who have reflux symptoms in the absence of endoscopic damage, but it is not clear that these patients necessarily have reflux disease. They may have hypersensitive esophagus or functional heartburn (ie, other conditions that mimic reflux disease). Therefore, these subsets of patients would not be expected to respond, or respond as well, to acid suppression therapy. That really confuses matters when trying to show incremental benefit from greater, more rapid, or more prolonged acid suppression when one is looking purely at the symptoms.

G&H How do safety and tolerability data for P-CABs compare with those for current GERD therapies?

DA Overall, it is probably too early to comment on long-term safety and tolerability. In the short term, data suggest that there is no significant difference between P-CABs and PPIs. In the long run, to the extent that adverse events or safety are related to acid suppression, medications that produce a greater duration or degree of acid suppression might be expected to have an increased incidence or prevalence of adverse events. Concern regarding long-term safety has been one of the challenges with acid suppression therapy, generally, and particularly so for PPIs, which have come under a lot of scrutiny for over the last 30 years. P-CABs are likely to face the same scrutiny as they enter clinical practice. However, I think that it is fair to say that PPIs as a class are very safe and the same is likely to be true for P-CABs. That said, it will take 30 years to have data for P-CABs that are comparable to all the data available for PPIs, which have been in use since the early 1990s.

G&H What role might P-CABs have in managing persistent reflux-like symptoms despite PPI therapy or in refractory GERD?

DA I think one needs to distinguish persistent symptoms from refractory GERD and there is evidence of marked variations in physicians' approaches to managing refractory reflux-like symptoms. I alluded to personalizing medicine earlier and I think that this is especially important for GERD patients who tend to be viewed as a homogeneous class of people with reflux disease, although it is well known that reflux can manifest in different ways and that the underlying pathophysiology differs as well. Health care providers need to determine for individual patients what causes their symptoms or their disease, and then how their treatment might be optimized to produce

symptomatic relief and healing. One of the challenges is that persistent reflux-like symptoms, as I said before, may not be caused by reflux and may require more extensive assessment. There are data and recommendations, for example, from the Lyon Consensus, suggesting that one should be looking at more physiologic testing to identify those patients on therapy who still have acid reflux into the esophagus as a basis for deciding how to treat.

Refractory GERD patients who still have reflux-like symptoms have not been well characterized. However, patients who have more severe EE at baseline (LA grade C/D) may require greater acid suppression such that healing may be better on treatment with a P-CAB that produces greater and more predictable acid suppression than, for example, a PPI. Because there are differences between PPIs with respect to cytochrome P450 metabolism, there may be variability of acid suppression that may become important in patients with more severe injury. P-CABs, which are less affected or are not affected by cytochrome P450 metabolism, may offer therapeutic benefits. Therefore, there may be greater predictability, which means in patients with severe disease or documented acid reflux on PPI therapy, P-CABs may be able to produce the greater, more predictable acid suppression that is needed for patients with more severe injury. With improved understanding of the pathophysiology and the response to current acid suppression, I think there are opportunities for use of P-CABs. However, it is not a foregone conclusion that everybody with refractory GERD or refractory reflux-like symptoms will do better on a P-CAB than a PPI.

P-CABs may supplant, replace, or augment PPIs in particular patient groups.

Another potential opportunity for P-CAB use is for patients who have NERD or possibly mild erosive disease, where there is no concern about the long-term consequences of continued reflux. In this case, on-demand therapy, or as-needed therapy, may be better with a medication that has a rapid onset of action and can therefore be taken intermittently rather than continuously. Continuous acid suppression therapy is probably more for patients with Barrett esophagus, which is a consequence of long-term acid peptic injury and repair. That is, arguably, a form of refractory GERD which, although it is not refractory EE or refractory symptoms, still merits surveillance and antireflux treatment. Patients with Barrett esophagus may require more prolonged acid suppression therapy to prevent disease progression and, again, P-CABs might offer a treatment tailored to the goals of reducing acid peptic injury and controlling symptoms.

G&H Have there been studies evaluating use of a P-CAB in combination with another therapy?

DA I am not aware of any data on the use of P-CABs in combination with another therapy such as mucosal protectants (eg, sucralfate), prokinetics (eg, prucalopride, domperidone, metoclopramide), or reflux inhibitors (eg, baclofen). I would add the caveat that none of these additional agents has shown consistent benefit when given in combination with PPI therapy.

G&H What do current guidelines on GERD recommend for P-CAB use?

DA The most recent North American guidelines on the diagnosis and management of GERD from the American College of Gastroenterology refer to the potential of P-CABs for treating GERD. As far as I am aware, the only formal reference to P-CAB therapy for GERD is in the Thailand guideline (2020) published in 2022. This guideline acknowledges the effectiveness of P-CABs and their noninferiority to PPIs for healing and maintenance of healed EE, and states that "P-CABs have a trend toward higher healing rates than PPIs in patients with severe EE." The level of evidence for the recommendation is High Grade and Conditional.

G&H How will P-CABs fit into clinical practice? Are they the next generation of PPIs?

DA I think that it is too early to know how P-CABs will fit into clinical practice. Their use will be guided by ongoing clinical research, but their uptake will also be affected by health system and insurance-reimbursement policies. P-CABs probably will prove to be as good as PPIs in terms of efficacy, and they may be beneficial in a subset of patients with acid-related disorders. However, strategies for diagnosing GERD need to be refined, both for determining which patients have acid-related symptoms and for defining the pathophysiology of their symptoms in order to work out which patients will benefit, specifically, from P-CAB therapy. P-CABs may supplant, replace, or augment PPIs in particular patient groups. There are, as I mentioned earlier, patients with severe disease that is unresponsive to current therapy and patients

with NERD, comprising more than 50% of GERD patients, who would welcome more rapid symptom relief from their treatment. So, there is a substantial number of people who might benefit from P-CAB therapy, but it goes without saying that more clinical studies are needed to define which types of patients or acid-related diseases would benefit from the unique properties of P-CABs and their pharmacology. I think there will be a role for P-CABs in practice if study investigators can identify the appropriate patient populations or subpopulations.

Having said this, I would not say that P-CABs are the next generation of PPIs. P-CABs are competing against PPIs, which revolutionized acid-suppression therapy. PPIs have a 30-year history of documented efficacy—and a level of efficacy that was unheard of prior to their existence—as well as a very good track record for safety, other than the concerns around acid suppression, which will apply equally to P-CABs at least for continuous therapy.

The overarching theme of our discussion is, I think, the fact that GERD should be viewed not as a single condition but as a range of underlying pathophysiologies and manifestations, which need tailored treatment. Once 60% to 80% of patients have improvement, the benefit beyond that comes down to understanding better what the disease is—understanding the nonresponders rather than the responders. The other point to highlight is that P-CABs as a class will exhibit common features but that they are likely, nonetheless, to show differences some of which may be clinically relevant. As in other areas, one will need to be careful to avoid the assumption that all P-CABs are exactly the same and that they will all produce identical outcomes.

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Suggested Reading

Armstrong D, Hungin AP, Kahrilas PJ, et al. Knowledge gaps in the management of refractory reflux-like symptoms: healthcare provider survey. *Neurogastroenterol Motil.* 2022;34(10):e14387.

Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW. Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the United States and Europe: randomized clinical trial. *Gastroenterology.* 2022;163(3):608-619.

GBD 2017 Gastro-oesophageal Reflux Disease Collaborators. The global, regional, and national burden of gastro-oesophageal reflux disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol.* 2020;5(6):561-581.

Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. *Gut.* 2018;67(7):1351-1362.

Hunt R, Armstrong D, Katelaris P, et al; Review Team. World Gastroenterology Organisation Global Guidelines: GERD Global Perspective on Gastroesophageal Reflux Disease. *J Clin Gastroenterol.* 2017;51(6):467-478.

Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2022;117(1):27-56.

Laine L, DeVault K, Katz P, et al. Vonoprazan versus lansoprazole for healing and maintenance of healing of erosive esophagitis: a randomized trial. *Gastroenterology*. 2023;164(1):61-71.

Maneerattanaporn M, Pittayanon R, Patcharatrakul T, et al. Thailand guideline 2020 for medical management of gastroesophageal reflux disease. *J Gastroenterol Hepatol*. 2022;37(4):632-643.

Wong N, Reddy A, Patel A. Potassium-competitive acid blockers: present and potential utility in the armamentarium for acid peptic disorders. *Gastroenterol Hepatol (N Y).* 2022;18(12):693-700.