ADVANCES IN UPPER GI DISORDERS

Current Developments in the Management of Upper GI Disorders

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On-Demand Therapy for Gastroesophageal Reflux Disease

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G&H What are the benefits of transitioning to a noncontinuous dosing strategy, specifically on-demand therapy, for gastroesophageal reflux disease?

RF On-demand therapy offers several advantages for managing gastroesophageal reflux disease (GERD), particularly from the patient's perspective. It is convenient and empowers patients by allowing them to decide when and how long to take the medication, giving them a sense of control. This approach has been shown to lower costs for patients and is generally considered cost-effective. Unlike proton pump inhibitor (PPI) therapy, which must be taken before meals for maximum effectiveness, on-demand potassium-competitive acid blocker (P-CAB) therapy can be taken as needed, regardless of meal timing. This flexibility reduces the guilt some patients feel when they struggle with adherence to strict dosing schedules. Additionally, it alleviates concerns—shared by both patients and physicians—about the potential adverse effects associated with long-term daily PPI use. Finally, on-demand therapy may lessen worries about rebound acid secretion, a phenomenon some believe may worsen symptoms after stopping PPIs, as the intermittent use reduces the likelihood of this effect.

G&H What attributes make an antireflux medication a good on-demand therapy for GERD?

RF There are 4 important attributes that are needed for a medication to be an excellent on-demand treatment for GERD. The medication has to provide potent acid suppression, rapid effect, an effect that is also durable, and flexibility in drug administration—patients must be able to take the medication whenever they need it. Looking at the current GERD therapies in the market, one can see that the classic on-demand medications, such as antacids and H2 blockers, are devoid of some of these attributes. Although they do work rapidly and demonstrate flexibility in administration, they do not provide any durable effect or potent acid suppression. Overall, of all the currently available drugs in the GERD space, P-CABs appear to have the best attributes for an on-demand therapy.

G&H What is the evidence for using this approach with PPIs?

RF Several studies have evaluated the use of PPIs as on-demand therapy for GERD, but many of these studies had limitations. One major issue is that PPIs have a delayed onset of action owing to their pharmacokinetics and pharmacodynamics, making them less ideal for rapid symptom relief. Additionally, the primary clinical endpoints used in these studies did not accurately capture the severity of heartburn that prompted patients to take medication or how well the treatment alleviated those symptoms. The most commonly used endpoint—discontinuation of treatment owing to inadequate heartburn control—was not a validated clinical measure, yet it was frequently applied. Another commonly used endpoint was average weekly antacid consumption, which lacked specificity. Despite these limitations, studies comparing on-demand PPI therapy with placebo demonstrated that patients found on-demand use appealing. Many patients were satisfied with this approach and preferred to continue it rather than stop treatment altogether. Over a 6-month period, patients using PPIs on demand required only 22%

to 43% of the total pills they would have used with daily therapy. For those who continued on-demand treatment, the approach significantly reduced their overall PPI intake compared with daily use. However, when on-demand therapy was compared with continuous daily PPI use, results showed that although patients appreciated the flexibility of on-demand therapy, they experienced more frequent symptoms. Consequently, quality-of-life scores were higher among patients using PPIs continuously. This is likely because on-demand therapy requires patients to experience symptoms before taking medication, making symptom occurrence an accepted part of this treatment approach. In contrast, patients on daily therapy aim to prevent any symptoms altogether.

G&H What is the evidence for using this approach with P-CABs?

RF Several studies have assessed the value of P-CABs as an on-demand treatment for GERD. A study that was conducted in the United States compared the use of a P-CAB as an on-demand treatment vs placebo in patients with nonerosive reflux disease (NERD) who initially received daily full-dose (20 mg) vonoprazan (Voquezna, Phathom Pharmaceuticals) for 1 month. This study included 3 treatment arms that used vonoprazan at different doses and 1 arm that used placebo. The clinical endpoints in this study were complete resolution of symptoms within 3 hours after drug consumption and sustained resolution of symptoms within the first 24 hours after drug initiation. These clinical endpoints are much more relevant and valuable than the ones used in the PPI studies. The 3 vonoprazan arms demonstrated a superior effect over placebo on patients' heartburn after only 1 hour of drug administration. In addition, the study showed that the superior effect of the 3 arms of vonoprazan was sustained over 24 hours as compared with the placebo arm.

This strategy involves patients taking medication in response to symptoms, meaning that patients accept a certain level of discomfort as part of this therapeutic approach.

G&H How do the different pharmacologic options compare?

RF Few studies have directly compared P-CABs with PPIs for on-demand treatment of GERD. One recent study compared the effect of tegoprazan 50 mg (K-Cab, HK inno.N) vs esomeprazole 20 mg as an on-demand treatment in patients with GERD (NERD or erosive reflux disease). At baseline, all patients demonstrated response to 4 to 8 weeks of once-daily PPI therapy. Tegoprazan demonstrated superior symptom control over esomeprazole within the first 30 minutes after drug administration. This superior effect was maintained during the first 3 hours after drug consumption. However, the study was small, with only about 35 patients in each group. Larger, well-designed studies are needed to confirm whether P-CABs are more effective than PPIs for on-demand GERD therapy.

G&H Which patients with GERD are not suitable for self-directed medical treatment on an on-demand basis?

RF Patients with erosive esophagitis, specifically those with grade C and D, are definitely not suitable candidates for on-demand treatment. Patients with complications of GERD (eg, peptic stricture, esophageal ulcer, or Barrett esophagus) are not suitable candidates, as these patients require continuous treatment. Also, on-demand treatment is not suitable for patients with frequent symptoms, regardless of GERD phenotype. However, most patients with GERD do not fall into any of these categories and consequently are good candidates for this therapeutic strategy. Patients with NERD who represent the vast majority of those with GERD and patients with grade A and a subset of those with grade B erosive esophagitis are all good candidates for on-demand treatment.

G&H What is the impact of on-demand therapy vs continuous therapy on symptom burden and health-related quality of life?

RF Understanding the on-demand approach is essential. This strategy involves patients taking medication in response to symptoms, meaning that patients accept a certain level of discomfort as part of this therapeutic approach. It is best suited for patients who experience symptoms infrequently or have episodic flare-ups with periods of remission. Symptom patterns can vary over time—patients may go through phases with frequent symptoms and periods of minimal or no symptoms. During these low-symptom periods, patients may switch from continuous to on-demand therapy using the same

medication. As mentioned earlier, studies have shown that compared with an on-demand approach patients on daily PPI therapy generally report better quality of life likely because they experience fewer or no symptoms. In contrast, patients using PPIs on demand tend to tolerate a certain level of symptoms, which can lower their perceived quality of life. Notably, there are currently no quality-of-life data from P-CAB studies. It will be important to see whether future P-CAB trials reveal different outcomes compared to what has been observed with PPIs.

G&H Could you provide a clinical scenario or guidance on how best to implement this strategy in practice and how long to try it?

RF The on-demand approach should not be confused with occasional over-the-counter use of antacids or H2 blockers. On-demand therapy is a structured strategy, particularly suitable for patients with NERD and those with a low grade of erosive esophagitis. These patients may begin treatment with daily medication at the approved dosage. After about 4 to 8 weeks, if their symptoms have markedly improved, they can transition to on-demand use.

In a study my colleagues and I presented at the 2024 American College of Gastroenterology annual meeting, we found that the patients who initially took a P-CAB daily for 4 weeks and then switched to on-demand therapy experienced fewer symptoms during the on-demand period than before starting daily treatment (at baseline). Once symptom frequency decreases, patients can try the on-demand approach. If symptoms become more frequent or severe, they can resume daily therapy. Later, if symptoms become infrequent again, they may switch back to on-demand use. This ability to alternate between daily and on-demand regimens provides significant flexibility for long-term GERD management. A key principle of on-demand therapy is that patients should not take more than one dose per day.

G&H What further research is needed on this topic?

RF As mentioned earlier, more comparative trials are needed to determine whether P-CABs are truly superior to PPIs when taken in an on-demand fashion. These differences must be validated in larger, real-world clinical studies. In addition, quality-of-life studies involving P-CABs—similar to those conducted with PPIs—are needed to better understand patient outcomes.

Rather than continuing to compare daily treatment with on-demand treatment, which are distinct approaches serving different patient needs, future research should focus more on long-term outcomes, such as the risk of adverse events and disease progression with on-demand therapy. Such studies are essential to reassure both physicians and patients that using acid-suppressive therapy on demand will not lead to worsening of disease. While overall adverse events have been reported to be low with on-demand therapy, even with P-CABs, there is some level of concern by both patients and physicians alike. For example, studies have shown that gastrin levels after 6 weeks of on-demand therapy were not significantly different from those seen with placebo. There is also a need for a more standardized framework for transitioning between daily and on-demand therapy. Clear guidance on when and how to shift between these regimens would improve clinical implementation and patient confidence.

With the introduction of P-CABs, patients now have the potential to personalize their treatment—switching between daily and on-demand use as their symptoms fluctuate. As more P-CABs become available and widely adopted, on-demand P-CAB therapy could become a true game changer. Currently, PPIs are intended for daily use, and patients who do not adhere to this regimen are often labeled as noncompliant. However, studies have shown that within 30 days of being prescribed a once-daily PPI, about 50% of patients begin taking it on demand. By 3 months, that number rises to 70%. In reality, many patients are already practicing a form of on-demand therapy on their own. What we have now is a medication that works reliably in an on-demand setting—giving patients effective symptom control without the guilt over missed doses, and with the flexibility they clearly want.

Disclosures

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Suggested Reading

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