

Is It Time for Noncontinuous Therapy for Gastroesophageal Reflux Disease?

Steve D'Souza, MD, Sharon Udemba, MD, and Ronnie Fass, MD

The Esophageal and Swallowing Center, Division of Gastroenterology and Hepatology, MetroHealth System and Case Western Reserve University, Cleveland, Ohio

Corresponding author:

Dr Ronnie Fass

Case Western Reserve University

MetroHealth Medical Center

2500 MetroHealth Drive

Cleveland, OH 44109

Tel: (216) 778-3145

Fax: (216) 957-8410

E-mail: ronnie.fass@gmail.com

Abstract: Gastroesophageal reflux disease (GERD) is a chronic disorder characterized by the reflux of gastric contents into the esophagus, leading to symptoms and potential long-term complications such as Barrett esophagus and esophageal adenocarcinoma. Currently, there are various medical, endoscopic, and surgical therapeutic strategies for GERD. However, proton pump inhibitors (PPIs), which effectively suppress acid secretion but require daily administration, remain the mainstay of treatment. Noncontinuous therapy for GERD includes on-demand and different variations of intermittent administration of antireflux medication. Attributes that make an antireflux medication a good candidate for noncontinuous therapy for GERD include potent acid suppression, rapid effect, durability of antisecretory effect, and flexibility of administration. Noncontinuous therapy for GERD is appealing to patients because it is convenient, reduces cost, and alleviates concerns about complications of long-term PPI use. Patients with nonerosive esophageal reflux disease or low-grade erosive esophagitis who have episodic heartburn are probably best suited for such treatment. Although PPIs have been shown to be efficacious as on-demand or intermittent therapy for GERD, their usefulness as on-demand treatment for episodic heartburn has been limited by their slow maximal effect on intragastric acid secretion. In contrast, potassium-competitive acid blockers (P-CABs) demonstrate the pharmacokinetic and pharmacodynamic characteristics that make this class of drugs a good candidate for noncontinuous treatment of GERD. Early studies using P-CABs for noncontinuous treatment of GERD have demonstrated promising results. Future studies are needed to further establish the value of P-CABs for such a therapeutic approach. This article reviews the current evidence on the use of PPIs and P-CABs in noncontinuous therapy for GERD.

Keywords

Potassium-competitive acid blockers, noncontinuous therapy, gastroesophageal reflux disease, on-demand therapy, intermittent therapy, proton pump inhibitors

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.¹ Some of the complications of GERD include esophageal ulcer, peptic stricture, Barrett esophagus, and esophageal adenocarcinoma.² Between 10% and 20% of the adult population of the Western world experience symptoms of

Table 1. Treatment Strategies for Gastroesophageal Reflux Disease

Regimen	Definition
Continuous use	Once- or twice-daily dosing until discontinued
Intermittent use	Short-course dosing of 7 days or 14 days following symptom onset (once daily) Alternative to daily dosing (standard dose every other day, weekdays only, weekends only)
On-demand use	Patient initiation of medication at onset of symptoms and discontinuation after symptom resolution No more than standard dose per 24 hours is expected

GERD, leading to a substantial economic burden from both direct and indirect costs.³ Furthermore, in the United States, the annual expenditure of proton pump inhibitor (PPI) therapy is high, estimated at \$19.99 billion in 2016 to 2017.⁴ PPIs have been widely adopted as the most effective treatment strategy for both nonerosive esophageal reflux disease (NERD) and erosive esophagitis because they provide good symptom control, healing of erosions, and prevention of disease relapse. However, up to 75% of patients with NERD will experience symptomatic relapse, and up to 90% of patients with erosive esophagitis have mucosal inflammation relapse within 6 months of discontinuing PPI treatment.^{5,6} This has led to many patients requiring long-term treatment to maintain adequate symptom control and, in the case of patients with erosive esophagitis, mucosal healing. The potential adverse events associated with long-term PPI therapy, such as *Clostridioides difficile* colitis, pneumonia, bone fracture, and mineral and vitamin malabsorption, have raised concerns among patients and physicians alike.⁷

Noncontinuous antireflux treatment is a highly attractive therapeutic strategy for patients with GERD who require long-term control of their symptoms.⁸ Noncontinuous antireflux treatment includes on-demand use and various iterations of intermittent use. This type of therapeutic strategy is associated with several advantages, including reduced cost, improved compliance, patient sense of control, and reduced concerns related to adverse events as a result of daily PPI consumption. Multiple studies have demonstrated the tendency of patients to self-deescalate PPI dosing to as-needed use.^{9,10} Furthermore, more recent GERD treatment guidelines favor adoption of a noncontinuous treatment strategy in a subset of patients with mild erosive esophagitis or those

with NERD with episodic heartburn.^{2,11}

PPI on-demand therapy is commonly used by patients with GERD despite limited clinical value. Presently, there is no US Food and Drug Administration (FDA) approval for an on-demand therapy for any of the available PPIs in the United States. In contrast to PPIs, potassium-competitive acid blockers (P-CABs) have pharmacokinetic and pharmacodynamic characteristics that make them good candidates for noncontinuous therapy for GERD. The P-CABs are highly potent, demonstrate rapid and durable effect, and have a flexible time for administration.

This article summarizes the current evidence for on-demand and intermittent therapy with PPIs and P-CABs and assesses the advantages, disadvantages, and overall effectiveness in managing GERD with both therapeutic strategies.

Noncontinuous Therapy for Gastroesophageal Reflux Disease

Noncontinuous therapy for GERD involves the use of antireflux pharmacologic therapies such as PPIs for a limited duration in order to achieve symptomatic relief. This approach is highly appealing to patients because it allows them to control the number of pills taken, reduce cost, and decrease concerns regarding adverse events owing to chronic daily use.¹² There are 2 forms of noncontinuous treatments: on demand and intermittent (Table 1).¹³ On-demand therapy is a patient-driven therapeutic approach, where patients determine when to start treatment (usually triggered by GERD-related symptoms) and how long to continue treatment. In the case of PPIs, it is expected that patients will not consume more than a standard dose over a period of 24 hours in response to symptoms, although the value of a double-dose PPI given on demand at one time has not been assessed. Intermittent therapy is a physician-driven therapeutic strategy, where patients are instructed to take their antireflux medication in response to GERD-related symptoms for a predetermined duration. The duration for intermittent therapy is decided by the treating physician, and it commonly lasts 1 to 2 weeks at a time. However, there are many variations of intermittent therapy, eg, every other day and weekends only. Some providers even consider on-demand therapy as a type of intermittent treatment. As with on-demand therapy, patients receiving intermittent therapy are instructed to consume not more than 1 PPI per day.

Noncontinuous therapies offer important advantages to patients and physicians alike. The main advantages are cost-effectiveness owing to reduction in overall pill burden and side effects and better adherence, all leading to

Table 2. Randomized Controlled Trials Utilizing On-Demand or Intermittent Dosing of PPIs

Study	Country/countries	Population	Methods	Results
Talley et al ³⁶ 2001	Denmark, Finland, Norway, Sweden	342 patients NERD Symptom resolution with 4 weeks of PPI	Esomeprazole 20 mg on-demand or placebo for 6 months	Higher discontinuation owing to symptoms within placebo group Higher use of antacids in placebo group
Talley et al ³⁷ 2002	United Kingdom, Ireland, Canada	721 patients NERD: symptoms within past 7 days	6 months of placebo, on-demand esomeprazole 20 mg, or on-demand esomeprazole 40 mg	Placebo: 42% unwilling to continue regimen Esomeprazole 20 mg: 7.8% unwilling to continue regimen Esomeprazole 40 mg: 11.3% unwilling to continue regimen
Hansen et al ³⁸ 2005	Norway	281 clinics, 2156 patients Reflux symptoms >3/7 days per week	4 weeks of esomeprazole 40 mg followed by randomization for 4 weeks to: esomeprazole 20 mg continuously or on-demand, or ranitidine 150 mg twice daily continuously	Continuous esomeprazole had the highest patient satisfaction and symptomatic relief. Ranitidine had the lowest patient satisfaction and relief. On-demand esomeprazole had intermediate patient satisfaction
Juul-Hansen, Rydning ³⁹ 2009	Norway	63 patients NERD: 3 months of symptoms, normal endoscopy	On-demand ranitidine 75 mg or on-demand lansoprazole 15 mg for 6 months	Ranitidine: 54.8% with treatment failure Lansoprazole: 12.5% with treatment failure
Kobeissy et al ⁴⁰ 2012	Lebanon	83 patients NERD	Rabeprazole 20 mg twice daily on-demand or ranitidine 300 mg twice daily on-demand	No difference in symptom scores or number of pills taken
Nagahara et al ⁴¹ 2015	Japan	117 patients New-onset GERD and recurrent GERD, reflux symptoms and endoscopy with LA grades A-D or minimal esophagitis	Omeprazole 20 mg daily for 8 weeks, then randomized to continuous or on-demand dosing for 24 weeks	In new-onset GERD, patients had better symptom-free response to continuous dosing early but lost benefit with time In recurrent GERD, patients had better symptom-free response with continuous dosing New-onset GERD patients had improved endoscopic healing (88.2%) compared with those with recurrent GERD (56.7%)
Bayerdörffer et al ²⁴ 2016	Austria, France, Germany, South Africa, Spain	598 patients NERD Completed 4 weeks of esomeprazole 20 mg daily	Esomeprazole 20 mg on-demand or esomeprazole 20 mg continuously for 6 months	On-demand use was noninferior in symptomatic control and total medication use 5% of on-demand group developed erosive esophagitis vs none of the continuous use group
Cho et al ⁴² 2018	Korea	80 patients GERD, upper endoscopy with LA grades A-D or minimal esophagitis Completed 8 weeks of PPI	Esomeprazole 40 mg on-demand or esomeprazole 20 mg continuously for 12 weeks	No significant difference in symptom control or patient satisfaction between groups
Jung et al ⁴³ 2023	Korea	25 institutions, 304 patients NERD or LA grades A and B esophagitis	Run-in period: continuous pantoprazole 40 mg for 4 weeks then pantoprazole 20 mg on-demand or continuous maintenance for 24 weeks	Continuous therapy: 36.1% unwilling to continue On-demand therapy: 45.9% unwilling to continue Better GERD symptom scores and higher gastrin levels with continuous treatment

GERD, gastroesophageal reflux disease; LA, Los Angeles; NERD, nonerosive esophageal reflux disease; PPI, proton pump inhibitor.

increased patient satisfaction.¹⁴ In addition, patients feel in control of their disease management, especially when using the on-demand approach. However, these treatment strategies are not appropriate for all GERD patients. Patients with erosive esophagitis Los Angeles (LA) grades B to D, peptic stricture, or Barrett esophagus should not be considered for noncontinuous treatment with antireflux medications. In addition, the main premise behind on-demand treatment is for a patient to consume an anti-reflux medication only after a GERD-related symptom has developed. This type of therapeutic approach takes into consideration that patients will experience a certain level of symptom burden that may affect their overall quality of life.¹⁵ Consequently, noncontinuous treatment should be entertained in patients with episodic heartburn and thus should be avoided in patients with daily or frequent episodes of GERD-related symptoms. Another important concern with noncontinuous therapy is patient compliance, as many patients with GERD experience symptomatic relapse after stopping their medication.¹⁴ Another potential disadvantage is the increased complexity of the patient's medication regimen. On-demand dosing may be relatively intuitive for some patients, whereas intermittent dosing may be difficult for some patients to incorporate into their schedule and a more defined regimen may be helpful.¹⁶ Additionally, the availability of on-demand medications may lead to medication overuse, even for non-GERD-related symptoms. Lastly, rebound acid hypersecretion is probably an infrequent problem in on-demand treatment with a PPI. This was demonstrated in one study in patients with NERD.¹⁷

Proton Pump Inhibitors

The effectiveness of noncontinuous PPI therapy for GERD management has been investigated through a number of studies. One systematic review and meta-analysis evaluated 10 randomized controlled clinical trials comparing on-demand PPI therapy vs placebo or continuous PPI treatment in GERD patients.¹⁸ The authors concluded that on-demand therapy with currently available PPIs such as esomeprazole is more effective than placebo or daily PPI for the long-term management of patients with NERD, mild erosive esophagitis, and uninvestigated GERD. On-demand therapy provided adequate symptom control and improved quality of life. Notably, a significantly higher number of patients were willing to continue using on-demand PPI treatment compared with the alternative therapy that was studied. Adherence to treatment and patient satisfaction were also higher with on-demand than with continuous PPI treatment. In addition, on-demand PPI therapy was more cost-effective, saving up to two-thirds of daily drug doses,

resulting in substantial cost saving to patients. However, the main clinical endpoint of these studies was patients' willingness to continue with the studied treatment arm. In addition, none of the aforementioned studies assessed the efficacy of a PPI taken in response to a GERD-related symptom in relieving the index symptom. Furthermore, PPIs' pharmacokinetics and pharmacodynamics are not conducive for an effective on-demand treatment for GERD patients. PPIs require administration of at least 30 minutes before a meal to be effective, which affects flexibility of drug administration. PPIs reach maximum effect on intragastric pH within 5 days of daily drug administration, resulting in slow onset of action that may lead to patient use of rescue antacids when symptoms recur.^{19–21} The short half-life of PPIs (1–2 hours) affects durability of their effect after a single dose is given as part of an on-demand approach.

On-Demand Proton Pump Inhibitor Use

A number of studies have evaluated the efficacy, safety, and cost-effectiveness of on-demand PPI use for GERD (Table 2). A systematic review and meta-analysis assessed the efficacy of on-demand vs continuous (daily) PPI therapy in adult patients with GERD, including patients with NERD and erosive esophagitis who required PPI maintenance therapy.²² The primary outcome was treatment failure, defined as patients prematurely discontinuing the allocated maintenance therapy. Secondary endpoints included the proportion of patients achieving successful symptom relief, patient satisfaction with the maintenance therapy, pill usage per day, and the frequency of adverse events in both treatment groups. Eleven randomized controlled trials were analyzed. Treatment failure was observed in 9.1% of the patients in the on-demand PPI group and 7.3% in the continuous PPI group, with a risk ratio (RR) of 1.26 (95% CI, 0.76–2.07), indicating no significant difference between the 2 treatment groups. Pill usage per day was significantly lower in the on-demand group compared with the continuous group (risk difference, -0.52). There was no significant difference in patient satisfaction (RR, 0.97) and frequency of adverse events (RR, 1.02) between the 2 groups. One included study evaluated the effect on LA grades C and D erosive esophagitis in subgroup analysis, finding higher treatment failure (RR, 4.24) and lower symptom relief (RR, 1.37) with on-demand compared with continuous treatment.^{22,23} Overall, on-demand therapy showed similar efficacy to continuous daily therapy in the maintenance treatment of GERD, but continuous therapy was a better option for patients with LA grades C and D erosive esophagitis. Presently, it is not recommended to offer any type of noncontinuous treatment to patients with LA grades C and D erosive esophagitis.

A multicenter randomized study also compared the willingness of patients with NERD to continue treatment with on-demand vs continuous maintenance therapy for symptom control using esomeprazole 20 mg.²⁴ After initially treating 598 adult patients with NERD for complete symptom control with esomeprazole 20 mg for 4 weeks, the cohort was divided into 2 treatment groups: one receiving daily esomeprazole and the other receiving on-demand dosing for 6 months. The primary measured outcome was treatment discontinuation owing to dissatisfaction. Although the authors reported that 5% of the on-demand group developed reflux esophagitis with mucosal breaks vs none in the continuous group, it is likely that these patients had either low-grade erosive esophagitis that was missed on index endoscopy or an index endoscopy that was performed on antireflux treatment ($P < .0001$). However, in terms of willingness to continue treatment, on-demand treatment with esomeprazole 20 mg was noninferior to continuous maintenance treatment, and it resulted in reduced medication usage for patients with NERD who achieved symptom control with initial esomeprazole treatment.

The choice of PPI has also been investigated by several studies. In a randomized controlled trial, the authors compared the clinical efficacy of dexlansoprazole 60 mg with that of esomeprazole 40 mg after a 24-week follow-up in patients with mild esophagitis.²⁵ Eighty-six adults with LA grades A and B erosive esophagitis were randomized to either once-daily treatment with dexlansoprazole or esomeprazole. Those who achieved complete symptom resolution after the initial treatment (8 weeks) were switched to an on-demand therapy until the end of 24 weeks with the same PPI. The study clinical endpoints included complete symptom resolution, the rate of symptom relapse, days to symptom resolution, sustained healing rate of erosive esophagitis, treatment failure rate, and the total number of tablets taken in 24 weeks. Overall, symptom relief at the end of 24 weeks was similar between both PPIs. However, patients on dexlansoprazole exhibited fewer days with reflux symptoms in the 24-week study period and better persistent improvement in the GERD Questionnaire score during the on-demand period compared with patients taking esomeprazole.

Finally, on-demand PPI therapy has been shown to be cost-effective as a maintenance treatment approach. In one cost-effectiveness analysis study, the authors determined that an 8-week course of PPIs for initial symptom relief, followed by on-demand PPI was the most cost-effective approach, when compared with lifestyle modifications, histamine type 2 receptor antagonist (H2RA) maintenance treatment, and continuous PPI maintenance treatment.¹⁴

Intermittent Proton Pump Inhibitor Use

Several studies evaluated the value of intermittent PPI therapy as a noncontinuous maintenance therapeutic strategy for GERD. Overall, intermittent PPI treatment provides the same clinical advantages as on-demand therapy. A multicenter clinical trial compared the overall efficacy of intermittent PPI use vs placebo for the maintenance of NERD.²⁶ A total of 388 patients with NERD were treated with rabeprazole 20 mg daily for 4 weeks. Those who achieved symptom relief were randomized to 6 months of intermittent therapy with 7 to 14 days of either rabeprazole or placebo for symptom recurrence. The investigators concluded that intermittent rabeprazole maintenance therapy was associated with more heartburn-free days and nights, fewer patient discontinuations of medication, and decreased use of daily antacids compared with the placebo arm.

Studies comparing intermittent maintenance use of PPIs with H2RAs have also been conducted. A randomized controlled multicenter clinical trial compared omeprazole vs ranitidine as intermittent therapies for NERD or mild to moderate erosive disease.²⁷ Patients were treated for 2 weeks with omeprazole 10 mg daily, omeprazole 20 mg daily, or ranitidine 150 mg twice daily. At the end of the 2 weeks, patients who were asymptomatic or mildly symptomatic were followed for 12 months as part of the intermittent group. Patients who remained symptomatic continued on their respective medication for an additional 2 weeks, with omeprazole-treated patients either increased to or continued on 20 mg daily, and ranitidine-treated patients increased to a dose of 300 mg twice daily. After the additional 2-week period, patients who were asymptomatic or mildly symptomatic also entered the intermittent group. Patients in the intermittent group who redeveloped symptoms were started on omeprazole 20 mg daily for the remainder of the 12-month follow-up. PPI therapy was significantly better than H2RAs by the second week, with 40% and 55% of the patients on omeprazole 10 mg and 20 mg, respectively, achieving symptom resolution compared with 26% of those in the ranitidine group ($P < .001$). A comparable percentage of patients, 46% and 48%, in the omeprazole 10 mg and 20 mg groups, respectively, were able to complete intermittent therapy.

A pilot study evaluated 3 maintenance treatment modalities in 60 patients with mild symptomatic NERD.²⁸ After successfully completing a 4-week course of lansoprazole 30 mg daily, patients were randomized into 3 groups: lansoprazole 30 mg daily on-demand, lansoprazole 15 mg daily continuously, and lansoprazole 30 mg daily for 4-week courses during relapse (intermittent). The intensity of symptoms was assessed using a visual analog scale (VAS) at baseline (mean VAS, 2.8), after 4 weeks (mean

Table 3. Randomized Controlled Trials Utilizing On-Demand or Intermittent Dosing of P-CABs

Study	Country	Population	Methods	Results
Umezawa et al ³⁴ 2018	Japan	30 patients Prior LA grades A and B esophagitis in endoscopic remission Daily maintenance PPI	6 months of on-demand vonoprazan 20 mg	0% grade A esophagitis patients with relapse 21.1% grade B esophagitis patients with relapse Patient satisfaction and gastrin levels remained the same between vonoprazan and PPI
Hoshikawa et al ³³ 2019	Japan	30 patients with NERD with symptom control on PPI	8 weeks of on-demand vonoprazan 20 mg	No difference in patient satisfaction, symptoms, and gastrin levels when switched from continuous PPI to vonoprazan Median 11 tablets total taken during the 8-week study period
Matsuda et al ³⁵ 2022	Japan	122 patients LA grades A-D esophagitis Daily maintenance PPI	Vonoprazan 20 mg EOD and lansoprazole 15 mg EOD Randomized to 4 weeks of PPI then P-CAB or P-CAB then PPI	Vonoprazan had higher efficacy at both 4 weeks (96.7% vs 80%) and at 8 weeks (90.7% vs 81.7%) in controlling symptoms >6 days per week Vonoprazan had higher efficacy at both 4 weeks (93.3% vs 85.7%) and at 8 weeks (94.4% vs 76.7%) in controlling symptoms to <1 day per week
Fass et al ³¹ 2023	United States	Multicenter 207 patients with NERD ≥6 months of symptoms: frequency ≥4/7 consecutive days during screening	Run-in period: vonoprazan 20 mg daily for 4 weeks Randomized to on-demand 10 mg, 20 mg, 40 mg, or placebo for 6 weeks	Placebo: 27.3% episodes with symptomatic relief Vonoprazan 10 mg: 56% episodes with symptomatic relief Vonoprazan 20 mg: 60.6% episodes with symptomatic relief Vonoprazan 40 mg: 70% episodes with symptomatic relief

EOD, every other day; LA, Los Angeles; NERD, nonerosive esophageal reflux disease; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

VAS, 0.4), and then at 3, 6, and 12 months of therapy. On-demand therapy (VAS, 0.85, 1.0, and 1.0) and continuous therapy (VAS, 0.65, 0.65, and 0.5) showed similar efficacy at 3, 6, and 12 months, respectively. Intermittent maintenance therapy demonstrated the lowest efficacy in controlling symptoms (VAS, 1.1, 1.55, and 1.65 at 3, 6, and 12 months, respectively) compared with the other 2 groups ($P<.05$). Cost-benefit analysis was also performed, revealing that intermittent therapy was the cheapest option among the 3 therapeutic strategies.²⁸ In contrast, on-demand therapy was intermediate in cost compared with continuous and intermittent treatment. This suggests that intermittent PPI use, although effective as a maintenance treatment strategy, is not as effective as on-demand therapy, which provides comparable symptom control to continuous use while being 30% cheaper. However, this is a relatively small study and additional studies with larger patient populations are needed to support these findings.

Potassium-Competitive Acid Blockers

P-CABs are a novel class of acid suppressants that have shown great promise as candidate medications for noncontinuous therapy in the management of GERD. They are currently available in many countries in Asia and South America. Vonoprazan (Voquezna, Phathom Pharmaceuticals) is the first FDA-approved P-CAB in the United States for both erosive esophagitis and eradication of *Helicobacter pylori* infection. There are other P-CABs in different phases of clinical trials that may also enter the market in the near future.

P-CABs demonstrate different pharmacokinetics and pharmacodynamics than PPIs. They have a long half-life of 3.7 to 10.3 hours, which is significantly longer than the half-life of PPIs (1-2 hours).²⁹ In addition, P-CABs have a rapid onset of action, reaching maximum effect on intragastric pH within 30 to 45 minutes of

drug administration and are able to maintain this level of acid suppression for a period of 24 hours. Moreover, P-CABs are not prodrugs like PPIs and do not require activation and thus administration prior to a meal. The aforementioned makes P-CABs good candidates for intermittent or on-demand treatment of GERD. In addition, they demonstrate all 4 attributes (rapid effect, potent acid suppression, durable effect, and flexible time of administration) needed for a medication to succeed as a noncontinuous treatment for GERD.

Early work has indicated that noncontinuous therapy is more effective with P-CABs than with PPIs. Although no difference in the prevalence of adverse events was noted when P-CABs were compared with PPIs, concerns have been raised regarding a higher increase in gastrin levels with P-CABs vs PPIs.³⁰ However, early studies in patients treated with noncontinuous P-CABs have demonstrated gastrin levels within the normal range.³¹ Interestingly, a continuous daily treatment study that compared a P-CAB with a PPI did not show significant effect of the P-CAB on the gastric mucosa during a 32-week period or any significant difference in gastrin levels.³²

On-Demand Potassium-Competitive Acid Blocker Use

Several studies have assessed the value of P-CABs, primarily vonoprazan, as an on-demand therapy for GERD (Table 3). In a phase 2 randomized controlled trial, the authors investigated the safety and efficacy of different doses of on-demand vonoprazan vs placebo in treating symptomatic NERD.³¹ A total of 207 patients with NERD were enrolled in the study. The study demonstrated that on-demand vonoprazan therapy at all doses (10 mg, 20 mg, and 40 mg) was significantly better than placebo in providing rapid and sustained (up to 24 hours) relief from heartburn episodes, at 56.0%, 60.6%, and 70.0%, respectively, in a dose-dependent fashion compared with 27.3% for placebo ($P < .0001$). Adverse effects were similar among the different arms of the study, and gastrin levels were within the normal range at the end of the on-demand period. The study also found that vonoprazan-treated patients took fewer rescue antacids than placebo patients.

One study investigated the efficacy of on-demand therapy with 20 mg of vonoprazan compared with prior continuous PPI use in 30 patients with NERD over an 8-week period.³³ There was no significant difference in patients' satisfaction scores, symptom resolution, or measured gastrin levels before and after therapy. The study concluded that on-demand therapy with vonoprazan 20 mg was equivalent to continuous PPI maintenance therapy. Patients with NERD taking on-demand therapy required a median of 11 tablets (19.6% usage) during the 8-week treatment period, indicating that reflux symptoms

were episodic, making on-demand therapy an appealing therapeutic approach.

Another study has also demonstrated the efficacy of on-demand P-CAB therapy when compared with continuous PPI treatment. A study of 30 patients with mild erosive esophagitis (LA grades A and B) on maintenance or continuous PPI therapy evaluated the use of vonoprazan 20 mg taken only with reflux symptoms over a period of 24 weeks.³⁴ Although some (21%) patients with LA grade B erosive esophagitis had relapsed, both satisfaction scores and gastrin levels were comparable. Notably, a median of 33 pills were taken by the on-demand group during the study period, suggesting 135 saved doses.

Vonoprazan and possibly the other P-CABs approved outside the United States appear to be good candidates for on-demand therapy in the management of GERD. Further research is needed to monitor long-term safety and durability of treatment response.

Intermittent Potassium-Competitive Acid Blocker Use

Very few studies assessed the value of intermittent P-CAB use in patients with GERD. In a multicenter open-label 2-period randomized cross-over study, the authors assigned patients with erosive esophagitis to either vonoprazan-lansoprazole or lansoprazole-vonoprazan groups.³⁵ The first group received vonoprazan 10 mg for the first 4 weeks and then lansoprazole 15 mg for the next 4 weeks both administered once every other day. The second group received lansoprazole first followed by vonoprazan during similar time durations. A total of 122 patients participated in this study. The study found that vonoprazan was more effective than lansoprazole when comparing their intermittent administration as maintenance therapy for erosive GERD, including heartburn and gastric acid reflux symptoms. In symptom diaries, GERD symptom scores significantly improved following vonoprazan treatment. Given the results of this study, transition to maintenance treatment with a P-CAB may be a viable and cost-effective option. However, more studies are needed to determine the most effective scheduling of P-CABs as an intermittent therapy.

Conclusion

PPIs are currently the mainstay of GERD treatment. However, continuous use of PPIs presents a number of challenges, including adherence, cost, and the potential risk of short- and long-term adverse events. Transition to a noncontinuous dosing strategy, whether intermittent or on-demand use, reduces total pill burden, provides cost savings, results in excellent symptom control in patients with episodic heartburn, reduces the likelihood of adverse events, and may be noninferior to continuous therapy in

generating sustained treatment response.

When compared with PPIs and even to H₂RAs and antacids, P-CAB therapy demonstrates all needed pharmacokinetic and pharmacodynamic attributes that make any medication a good candidate for noncontinuous treatment of GERD. Those attributes include rapid effect, potent acid suppression, durable effect, and flexible time of administration.

There is a large body of literature supporting the use of PPIs as an effective on-demand or intermittent therapy for GERD. Similarly, there is a growing number of publications suggesting that P-CABs are also good noncontinuous treatment for GERD. Early studies suggest that P-CABs maybe better than PPIs when comparing efficacy in noncontinuous treatment of GERD. It is also possible that P-CABs may be the first FDA-approved antireflux medication for noncontinuous treatment of GERD.

Not all GERD patients may benefit from noncontinuous therapy. Patients with NERD or those with low-grade erosive esophagitis reporting episodic heartburn are probably the best candidates for such treatment. However, while initial studies with P-CABs have been promising, more data are needed to determine the value of this new class of medications as a noncontinuous treatment strategy for GERD.

Disclosures

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