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NEUROMUSCULAR DISORDERS OF THE GASTROINTESTINAL TRACT (S RAO, SECTION EDITOR)

Novel Therapies for Gastroesophageal Reflux Disease: Beyond Proton Pump Inhibitors

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Abstract

Purpose of Review Despite the many areas of unmet needs in gastroesophageal reflux disease (GERD), proton pump inhibitors (PPIs) remain the cornerstone of medical therapy. However, since their introduction, the therapeutic limitations of PPIs in GERD management have been increasingly recognized.

Recent Findings In this review we discuss the new medical, endoscopic, and surgical therapeutic modalities that have been developed over the last decade. They include the potassium-competitive acid blockers (P-CABs) which provide a rapid onset, prolonged, and profound acid suppression, mucosal protectants which promote the physiological protective barrier of the esophageal mucosa, new prokinetics and neuromodulators. There are growing numbers of novel therapeutic endoscopic techniques that are under investigation or were recently introduced into the market, further expanding our therapeutic armamentarium for GERD.

Summary The development of diverse therapeutic modalities for GERD, despite the availability of PPIs, suggests that there are many areas of unmet need in GERD that will continue and drive future exploration for novel therapies.

Keywords Heartburn · Gastroesophageal reflux disease · Proton pump inhibitor · Proton pump · Lower esophageal sphincter · Neuromodulators

Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. GERD is a common disorder with significant impact on patients' quality of life and healthcare utilization [1]. Gastroesophageal reflux disease has steadily increased since the 1990s especially in North America and East Asia (10–20% and 2.5–7.8%, respectively) [2, 3]. In the USA, GERD is one of the most frequently encountered gastrointestinal disorders in the outpatient setting [4], with 20% of the adult population experiencing weekly symptoms and 7% reporting daily symptoms [5, 6]. While the gamut of GERD-related symptoms is very wide, typical manifestations include heartburn and/or regurgitation. Commonly, diagnosis is clinically based, and the treatment is usually empirical.

The three phenotypes of GERD are non-erosive reflux disease (NERD), erosive esophagitis (EE), and Barrett's esophagus (BE). Their response to treatments vary considerably [7].

Currently, pharmacologic, endoscopic, and surgical therapeutic modalities are available for the treatment of GERD. The proton pump inhibitors and histamine-2 receptor antagonists (H2RAs) are the most frequently prescribed medications in clinical practice for the treatment of GERD. Other less potent agents are generally used for mild or intermittent symptoms or as an add-on therapy. Those include, antacids, carafate, baclofen, alginate, and prokinetics.

The ultimate goals of therapy in GERD are the resolution of symptoms, healing of esophageal inflammation, maintenance,

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and thus, prevention of symptoms recurrence or relapse of esophageal inflammation and improvement of quality of life [8].

Thus far, PPIs are considered the mainstay of therapy for GERD. Due to their profound and consistent anti-secretory effect, which is unmatched by any other class of drugs, PPIs have been highly successful in healing erosive esophagitis, controlling symptoms, and preventing GERD-related complications such as esophageal ulcer, esophageal bleed, and peptic stricture. Overall, PPIs have been considered a very safe class of drugs, resulting in many patients receiving these medications long term. However, despite the success that PPIs achieved in controlling the different facets of GERD, there are still many areas of unmet need [9, 10]. Those include, advance erosive esophagitis (20–40% failure rate), non-erosive reflux disease (up to 40% failure rate), nighttime heartburn (38% failure rate), maintenance treatment (up to 30% relapse rate), and refractory GERD (up to 40%) [6, 11]. In addition, PPIs are not effective in post prandial heartburn and even today are still not approved for atypical or extraesophageal manifestations of GERD as well as GERD complications [12]. Importantly, chronic PPI treatments have been associated with variety of adverse events, raising concerns about their safety profile among physicians and patients alike.

Due to the aforementioned unmet needs, further research in alternative medical, endoscopic, and surgical therapeutic modalities have resulted in the development of promising novel therapies for GERD. This review will highlight the most recent and future pharmacological and non-pharmacological modalities that are currently available or under investigation for the treatment of GERD.

Pharmacological Treatment

Potassium-Competitive Acid Blockers (P-CABs)

Over the last three decades, several P-CABs have been developed for the purpose of acid suppression. This novel class of anti-secretory drugs has been shown to have a rapid onset of action, prolonged half-life and profound acid inhibitory effect as compared with PPIs (see Table 1) [20]. The potassium-competitive acid blockers bind competitively and reversibly to the potassium binding site of the H^+/K^+ -ATPase. They are immediately protonated, and accumulate at a much higher concentration than PPIs in the parietal cells' canaliculi (Fig. 1). In fact, P-CABs concentration in the parietal cells' canaliculi is 100.000-fold higher than in the plasma as compared with PPIs, which are only 1000-fold higher. In addition, P-CABs are able to bind to both the active and inactive forms of the ATPase pump resulting in a faster and longer duration of anti-secretory effect [21]. Early onset of action is due to the rapid rise of the P-CABs' peak plasma concentration [17]. In contrary to PPIs, the elimination of P-CABs is independent of cytochrome P450 CYP 2C19 metabolism, which further contribute to their increased potency [22].

In addition to enhanced potency, there are several advantages of P-CABs over the existing anti-secretory medications, that include full effect from the first dose, long half-life, duration of effect which is related to the half-life of the drug in the plasma, and ease of administration which is the ability of taking the drug unrelated to mealtime [13]. Interestingly, it was observed that some P-CABs have a gastric promotility effect by stimulating phase III migratory motor complex (MMC), which suggests an added benefit to acid suppression. The underlying mechanism of this effect is not entirely understood, but it may be an interesting phenomenon for future research [23, 24]. Presently, there are three P-CABs that are already available in Asia (Table 2) [26].

Among this novel group of acid suppressants, vonoprazan has been studied the most. Since its inception, it has demonstrated an excellent safety and tolerability profile similar to that of a regular PPI in short-term treatment. As with PPIs, long term P-CAB use has been associated with hypergastrinemia [18, 30]. It has been demonstrated that gastrin levels may reach values above 1000 pg/ml in patients receiving long term vonoprazan. In fact, levels of gastrin continue to rise over time and may double after 1 year of treatment as compared to those measured after 8 weeks [30]. Despite such a dramatic rise in gastrin levels overtime, there has been no documentation of a significant effect on gastric neuroendocrine cells or pepsinogen levels. In addition, the reason for the continuous rise in gastrin levels overtime remains unknown. Other adverse events, similar to those reported with long term treatment of PPIs, such as, interference with nutrient absorption, increased risk for enteric infections, and travelers'

Table 1 The pharmacokinetics and pharmacodynamics differences between P-CABs and PPIs

	Mechanism [13, 14]	*T*max (h) [15, 16]	*T* ½ (h) [15, 16]	Maximal effect (day) [14, 17]	Nocturnal acid suppression [14, 18]	Effect of CYP2C19 [14, 18]	Acid stability [14, 19]	Meal effect [14, 19]
P-CAB	Binds competitively to the potassium binding site of H+/K + -ATPase	≤ 2 h	9 h	1	++	–	+	–
PPI	Covalent binding to H+/K + -ATPase	2–4 h	1–2 h	3–5	+	+	–	+

P-CAB potassium competitive acid blocker, *PPI* proton pump inhibitors

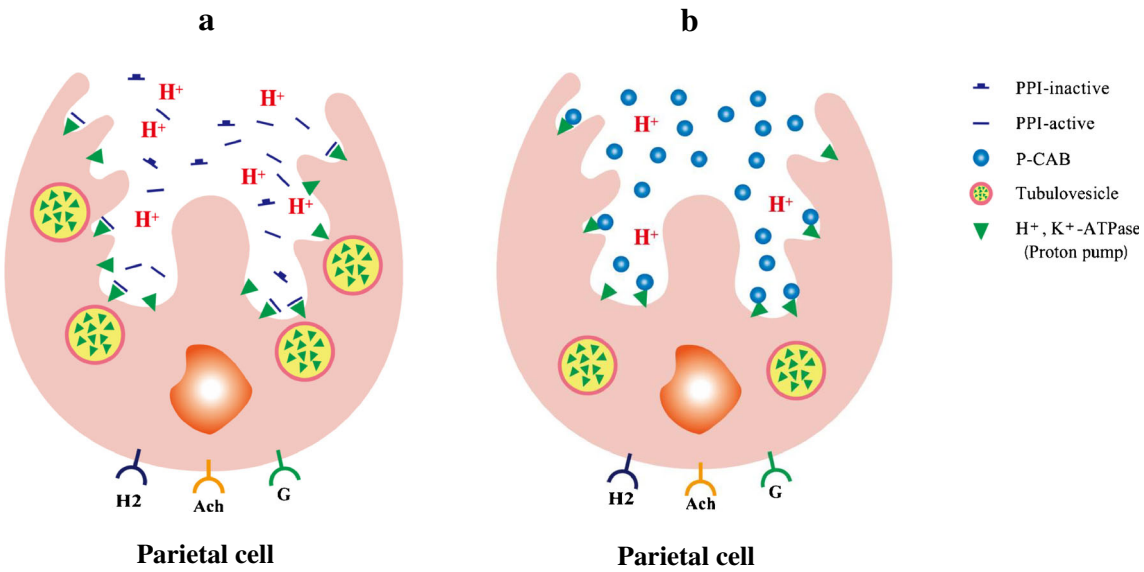

Fig. 1 *Mode of action of P-CABs as compared with PPIs.* The PPIs convert to their active form in acid milieu within the secretory canaliculi and bind covalently to H+/K+ -ATPases in a stimulated parietal cell (A). P-CABs accumulate in a high concentration in the secretory canaliculi, bind reversibly to H+/K+ -ATPases with no need for an acid milieu for drug activation (B) H_2 histamine, *Ach* acetylcholine, *G* gastrin

diarrhea, have also been suggested to affect patients receiving long term vonoprazan. Potassium competitive acid blockers might alter the gut-microbiome and increase the risk of enteric infections. These alterations were more observed with vonoprazan use, and they seem to be related to increase in lipopolysaccharide (LPS) biosynthesis, an endotoxin found in the outer membrane of Gram-negative bacteria, capable of inducing strong immunological responses [20, 31, 32].

Revaprazan (YH1885, Revanex®) is the first approved P-CAB that reached the market in 2007. The drug is indicated for the treatment of gastric ulcer, gastritis, and duodenal ulcer in South Korea and India [26]. Revaprazan rapidly and effectively inhibits gastric acid secretion. The drug increases percentage time of pH > 4 in a dose-dependent manner (reaches pH 5 within 2 h when using 200 mg per day). However, when revaprazan 200 mg daily was given to healthy male volunteers over a period of 7 days the mean intragastric pH was 3.3 and

Table 2 The pharmacodynamics and pharmacokinetics of available P-CABs or those under investigation

P-CAB	Chemical composition	Doses (mg)	T_{max} (h)	C_{max} (μmol/l)	AUC (μmol·h/l)	T ½ (h)	Day 1 pH > 4 holding time (%)	Day 7 pH > 4 holding time (%)
Revaprazan (YH1885) [25••]	Pyrimidine derivative	200	2.1 ± 1.3	361.4 ± 124.1	1343.1 ± 365.9	2.4 ± 0.2	NA	NA
Vonoprazan fumarate (TAK-438, Takecab® [25••, 26]	Pyrrole derivative	10	1.75	9.7 ± 2.1	60.1 ± 9.0	6.95 ± 1.03	38.4 ± 22.3	63.3 ± 8.7
		20	1.5	25 ± 5.6	160.3 ± 38.6	6.85 ± 0.80	63.3 ± 17.9	83.4 ± 16.7
Tegoprazan (CJ-12420) [27]	Benzimidazole derivative	100	0.8~1.8	0.81~1.10	0.91~0.93		70.4	62.3
		200		(log trans-formed)	(log trans-formed)	3.65~5.39	94.6	76.8
Linaprazan (AZD0865) [28]	Imidazopyridine derivatives	25	NA	NA	NA	NA	65.6 ± 20.8	NA
		50					74.3 ± 17.7	
		75					77.0 ± 18.3	
X842	a prodrug of linaprazan	NA	NA	NA	NA	NA	NA	NA
DWP14012 [29]	Pyrrole derivative	40–160	1.75–3.5	40.9 ± 17.3	452.8 ± 167.7	9.1 ± 1.2	80.5	87.4
KFP-H008	Pyrrole derivative	NA	NA	NA	NA	NA	NA	NA

P-CAB potassium competitive acid blocker, *PPI* proton pump inhibitors, *AUC* area under the curve

3.9 on the first and seventh day of treatment, respectively. The mean intragastric pH was noted to be less than 4 and the pH > 4 holding time was less than 12 h, findings similar or even inferior to those reported in PPI studies [33, 34]. A case-control study compared the efficacy of revaprazan and rabeprazole for the treatment of iatrogenic ulcers caused by endoscopic submucosal dissection (ESD) in patients treated for gastric neoplasia. Both drugs showed similar efficacy and safety profiles [35].

Beyond the acid suppression, revaprazan has two additional pharmacological effects, and they include gastroprotection due to increase in prostaglandin E2 and reduction in the production of leukotriene B4, as well as anti-inflammatory effect by regulating MAPK ERK1/2 signaling which is an important enzyme in the mucosal inflammatory response [36]. Furthermore, revaprazan was found to have a significant anti-inflammatory effect on gastric mucosa during Helicobacter pylori infection, by inactivating Akt signaling and NF-κB, cytokines that are implicated in cyclooxygenase-2 (COX-2) expression, which is pivotal in gastric inflammation development after *H. pylori* infection [37].

Vonoprazan fumarate (*TAK-438*, *Takecab*®) is a pyrrole derivative P-CAB that is approved in Japan since 2015 for the treatment of gastroduodenal ulcers, healing and prevention of erosive esophagitis, gastric protection in patients taking aspirin or non-steroidal anti-inflammatory drugs, and eradication of *Helicobacter Pylori* infection. Vonoprazan has a faster onset, greater potency, and longer duration of action than a PPI [25••, 38]. The half-life is about 7.7 h, pKa > 9, C_{max} 1.5 h, and metabolism of the medication is independent of CYP2C19. The percent pH > 4 holding time for vonoprazan 20 mg once daily is 63% on day 1 and 84% on day 7 [39]. It has the ability to inhibit the gastric proton pump even in neutral pH. This is in contrast to PPIs, which are prodrugs, and require activation by an acidic environment. Consequently, it is recommended to administer PPIs 30 min prior a meal to ensure drug activation. Vonoprazan on the other hand can be taken irrespective to meal time. The drug is currently undergoing phase III trials in Europe and the USA [33].

In a randomized, double-blind phase III clinical trial, vonoprazan 20 mg was compared with lansoprazole 30 mg in healing erosive esophagitis. The study demonstrated that vonoprazan was effective, well-tolerated, and non-inferior to lansoprazole, with similar healing rates at 8 weeks (92.3% and 91.3%, respectively). Furthermore, vonoprazan was demonstrated to provide excellent healing rates in patients with PPI-resistant erosive esophagitis, indicating the potential role of the medication in difficult to treat erosive esophagitis [40–42]. Vonoprazan was also evaluated in patients with NERD. In the first study, vonoprazan at doses of 10 mg or 20 mg once a day was equivalent to placebo in controlling GERD-related symptoms. However, the mean severity of heartburn score was significantly lower with both doses of vonoprazan as compared with placebo [43].

Tegoprazan (*CJ-12420*, *K-CAB*) is a benzimidazole derivative, approved, and marketed since July 2018 in South Korea for the treatment of erosive esophagitis and non-erosive reflux disease. In vitro and in vivo studies in rat model have shown that tegoprazan effectively inhibits the H+/K+ ATPase (80-folds higher) and suppresses gastric acid secretion faster than esomeprazole (pH 6.86 and pH 4.86 after 5 h of single dosing of 10 mg/kg tegoprazan and 30 mg/kg esomeprazole, respectively) [44]. In a randomized, double-blind, placebo-controlled, phase I trial, the safety and efficacy of tegaprazan were assessed in a single and multiple ascending doses and compared with the pharmacodynamic effect of esomeprazole 40 mg, in 56 healthy males. The study showed that the time to reach maximum pH after tegoprazan dosing was 1 h in contrast to esomeprazole that reached its maximum pH only after 4 h. The mean half-life (t1/2) ranged from 3.65 to 5.39 h, pKa 5.1, and time to C_{max} 1 h. The percent of holding time of pH > 4 over 24 h increased to 87% in a dose-dependent manner, and it was higher on day 7 than on day 1, with mean values of 54.3% and 68%, respectively. Tegaprazan was safe and well tolerated in a single and multiple doses [27]. Like other P-CABs, tegoprazan is also able to spontaneously induce the phase III migratory motor complex (MMC) [23].

In one study the effect of tegoprazan on erosive esophagitis was assessed in a multicenter, randomized double-blind, parallel-group design. A total of 302 patients with endoscopic confirmed erosive esophagitis were randomly assigned to Tegoprazan (50 or 100 mg) or esomeprazole 40 mg for 8 weeks of treatment [45]. The cumulative healing rates at week 8 were 98.9%, 98.9%, and 98.9% for tegoprazan 50 mg, 100 mg, and esopmeprazole 40 mg, respectively. Both doses of tegoprazan were non-inferior to esomeprazole and well tolerated.

Linaprazan (*AZD0865*) an imidazopyridine derivative with a short half-life and high-clearance rate. In preclinical and clinical studies, linaprazan showed rapid and prolonged suppression of acid secretion in a dose-dependent fashion. The drug inhibits acid secretion in a 100-fold lower dose than omeprazole [46]. In a double-blind, active control, randomized trial linaprazan was compared to esomeprazole 40 mg daily in healing erosive esophagitis over a period of 4 weeks. Healing rates were similar among both groups (AZD0865 and esomeprazole). Dose-dependent elevations in liver transaminases were seen in the linaprazan group, but not in the esomeprazole group [47].

Development of linaprazan was discontinued because of lack of additional healing effect when the drug was compared with standard dose PPI therapy and growing concerns about the safety profile of the medication [28, 47]. Currently a new formulation of linaprazan (X842, linaprazan, prodrug) is under investigation in phase II trial.

X842 (*linaprazan*, *prodrug*) is a prodrug of linaprazan, which is currently under development. X842 has long half-life (t1/2 = 10 h) and provides better 24-h intra-gastric pH control. This was demonstrated in a phase I trial which evaluated the safety and tolerability of the drug in healthy volunteers as a primary outcome using a single dose or multiple ascending dose design [48]. The X842 was safe and well tolerated by the participating subjects. No severe or serious adverse events were reported during the study. A clear dose-linearity was observed when both pharmacodynamic and pharmacokinetics parameters were assessed. The mean of median intragastric pHs at each dose of X842 was never below 4. As of April 2019, X842 is undergoing a phase II clinical trial at sites in Europe.

DWP14012 is a new potassium-competitive acid blocker (P-CAB) that is currently under clinical development. The DWP14012 inhibits acid secretion in a dose-dependent manner. The drug is able to suppress acid production similar or to a greater extent than vonoprazan. In a phase 1 clinical trial, the DWP14012 showed rapid and sustained suppression of gastric acid secretion with intragastric pH maintained above 4 for 24 h after single and multiple dosing. The gastric holding time pH > 4 after 80 mg and 160 mg of DWP14012 was 80.5 ± 8.4% and 91.3 ± 4.1%, respectively. The mean gastric pH-time for those who received DWP14012 was similar to those who received esomeprazole 40 mg. The drug reached C_{max} after 1–4 h, AUC > 1000 μg.h/L and half-life (T1/2) of 9 h. The drug was safe and well tolerated. The serum gastrin level was lower than that of vonoprazan and returned to normal range 48 h after drug cessation. No hepatotoxicity was observed [29].

KPF-H008 is a novel and potent P-CAB that is still under preclinical development. In animal experiments, KPF-H008 was found to be more effective with a longer anti-secretory effect when compared with lansoprazole. It's inhibitory effect on proton pumps was about 250 times stronger than lansoprazole and similar to vonoprazan. KPF-H008 at a dose of 1 mg/kg inhibited acid secretion by 60% during the first 3 h after administration with a long-lasting effect (> 48 h) [49].

Mucosal Protectants

Rebamipide (*Rebagen* ®, *Mucosta*®, *Rebagit*®) is an amino-derivative quinolinone that serves as a mucosal protectant. Currently, this agent is marketed in several countries in South-East Asia as an over-the-counter (OTC) compound for esophageal acid-related disorders. Rebamipide confer its effect by enhancing the production of prostaglandins (PG) in the gastric mucosa. Additionally, rebamipide functions as a scavenger of free reactive oxygen species (ROS) known to cause mucosal injury. Rebamipide induces the expression of prostaglandin EP4 (PGEP4) gene and epidermal growth factor (EGF) and its receptor thereby promoting the physiological protective barrier of the gut mucosa.

In a placebo-controlled trial that included 149 NERD subjects who failed PPI treatment, the authors were unable to demonstrate a significant effect of rebamipide over placebo on subject's symptoms [50]. Another randomized controlled trial evaluated the effect of either a combination of rebamipide with a PPI or PPI alone on healing of post endoscopic submucosal dissection ulcers with greater than 40 mm diameter. The authors demonstrated that the percent of subjects whose ulcer reached the scar stage was significantly greater in the combination group (68%) than the PPI alone group (35%) (p = 0.011) [51]. Furthermore, a recent in vivo study utilizing a rat model of GERD compared the effect of PPI alone to rebamipide with a PPI on tight junction proteins of the esophageal mucosa. The authors showed that the mean surface area of mucosal erosions, epithelial thickness, and leukocyte infiltration were lower in the PPI alone and PPI + rebamipide groups as compared to control untreated rats. However, expression of claudin-3 and -4 (integral membrane proteins and components of tight junction strands) was significantly higher in the combination group as compared to the control group [52].

Esoxx® (*Alfa Wassermann*, *Bologna*, *Italy*) this compound was developed in 2004 as an OTC medication for the treatment of GERD. It is a mixture of hyaluronic acid and chondroitin-sulfate suspended in a bio-adhesive carrier Lutrol® F 127 (poloxamer 407). It serves as an esophageal mucosal protectant barrier against gastric refluxate. In an in vitro study, using swine esophageal mucosa, the protective role of Esoxx® in preventing chemical injury was assessed by exposing the esophageal mucosa to different hydrochloric acid solutions in the presence or absence of pepsin. The study demonstrated that Esoxx® reduced the permeability of the mucosa and thus, provided protection against chemical injury [53]. In a randomized, double-blind, placebo-controlled trial, 154 patients with NERD were randomized to receive either Esoxx ® with standard-dose PPI or placebo with standard-dose PPI. The combination of Esoxx® and PPI was significantly more effective in improving GERD-related symptoms as compared to the combination placebo plus PPI (52.6% versus 32.1%, respectively) [54].

Transient Lower Esophageal Sphincter Relaxation (TLESR) Reducers

TLESR is considered to be the main underlying mechanism for gastroesophageal reflux in the majority of GERD patients (55–80%). It is in particular an important mechanism for gastroesophageal reflux in patients with NERD, where hiatal hernia, esophageal peristalsis, and lower esophageal sphincter abnormalities are highly uncommon [55]. Several receptors play a role in triggering TLESR, and their ligands have been

the focus of drug development [56]. They include, gamma-aminobutyric acid B ($GABA_B$), metabotropic glutamate receptor 5 (mGluR5), cannabinoid 1 (CB1), cholecystokinin (CCK), 5-hydroxytryptamine 4 ($5\text{-}HT_4$), muscarinic, and opioid.

Thus far, the development of compounds targeting the aforementioned receptors with the intention of significantly reducing the rate and duration of TLESRs has failed due to lack of significant efficacy over placebo and unacceptable side effects profile [57–66]. These include arbaclofen placarbil ($GABA_B$ agonist), lesogaberan ($GABA_B$ agonist), raseglurant ($mGluR_5$ antagonist), AZD2066 ($mGluR_5$ antagonist), rimonabant (CB1R antagonist), dronabinol (CB1 + CB2 agonist), and loxiglumide (CCK antagonist). Presently, the development of TLESR reducers, the first type of medications that specifically targeted the main underlying mechanism of GERD, has been halted. However, it is possible that in the future this attractive area of drug development may be reevaluated.

Prokinetics

Prokinetics have been proposed to improve GERD-related symptoms by different mechanisms including, enhancing esophageal peristalsis and thus, accelerating esophageal acid clearance, increasing LES basal pressure and accelerating gastric emptying. The clinical benefit of prokinetics as sole treatment for GERD has been modest at best. Moreover, their use has been hampered by various adverse effects [67].

Acotiamide (*Acofide*, *YM-443 and Z-338*) is currently approved in Japan for the treatment of functional dyspepsia. Acotiamide, a selective acetylcholinesterase inhibitor, suppresses the degradation of acetylcholine (ACh) that is released from the cholinergic nerve terminals [68]. Recently, the effect of acotiamide has been evaluated in GERD. In a randomized, placebo-controlled crossover trial 16 functional dyspepsia (FD) patients who failed PPI were randomized to either placebo or acotiamide for a period of 28 days in each therapeutic arm [69]. High-resolution impedance manometry revealed a significantly higher esophagogastric junction pressure, distal contractile integral, and highest distal contractile integral pressure in the acotiamide group as compared to placebo. The drug also significantly improved upper gut symptoms, esophageal primary peristalsis, and bolus transit. Another randomized, double-blind, placebo-controlled trial aimed to investigate the effect of adding acotiamide to PPI or vonoprazan refractory GERD patients (15 erosive esophagitis and 55 NERD) as compared with adding placebo to PPI or vonoprazan refractory GERD patients [70]. The authors demonstrated a significant improvement in the overall treatment effect (OTE) of either PPI or vonoprazan when acotiamide was added as compared to placebo (28.6% and 14.3%, respectively). In addition, acotinamide significantly reduced the total number of reflux episodes ($p = 0.001$).

Prucalopride, a first in class dihydro-benzofurancarboxamide, is a potent selective $5\text{-}HT_4$ receptor agonist with enterokinetic properties [71]. The drug is currently used for chronic constipation. However, several studies have suggested that the drug may have an effect on GERD. A prucalopride has been shown to reduce esophageal acid exposure and accelerates gastric emptying [72]. In addition, the drug has been shown to enhance primary peristalsis in patients with ineffective esophageal motility [73].

Pumosertag (*DDP733*) is a potent $5\text{-}HT_3$ receptor agonist with gastrointestinal prokinetic activities. DDP733 increased LES basal pressure in experimental animal models. In addition, DDP733 significantly reduced the rate of reflux events and increased the mean amplitude of distal esophageal contractions without changing the basal pressure in healthy human subjects. [55, 74]. Similar findings were recorded in patients with uninvestigated GERD, undergoing a standard refluxogenic meal [75].

Pain Modulators

The use of neuromodulators in GERD has been suggested to have value in patients with non-erosive reflux disease, where both gastroesophageal reflux and esophageal hypersensitivity play an important role in symptom generation [76••]. In addition, neuromodulators may have an additive role to PPI therapy in GERD patients who demonstrate an overlap with a functional esophageal disorder [77, 78]. The development of specific esophageal pain modulators have not been successful thus far, primarily due to lack of efficacy as compared to placebo. A good example is AZD1386, a transient receptor potential vanilloid 1 (TRPV1) antagonist, which failed to demonstrate an increase in esophageal pain perception threshold in healthy subjects or in patients with NERD and partial response to PPI treatment [79–82].

Prostaglandin E2 receptor antagonist, prostaglandin E2 (PGE2) exerts its biological action through several receptors, including EP1, which is considered to have a major role in pain processing and the development of hypersensitivity [83]. The EP-1 receptor antagonist (ONO8359), which reduced acid sensitivity in healthy volunteers, was studied in patients with non-erosive reflux disease, but the results of the study have yet to be published [84].

Non-Pharmacological Modalities

While medical therapy remains the mainstay of GERD treatment, a growing number of GERD patients and physicians alike have been looking for alternative non-medical therapeutic modalities [85]. Patients who developed side effects from medical therapy, poor compliance with medical therapy,

concerned or wish to discontinue chronic medical therapy, symptomatic with a large hiatal hernia (> 5 cm), have regurgitation as the predominant symptom, no interest in medical therapy and with abnormal pH test on maximal PPI dose may seek non-medical therapeutic modality for GERD [86]. At the same time, studies have demonstrated that there has been a marked decline in the number of GERD patients undergoing surgical intervention for GERD [87]. This also suggests that patients are interested in non-medical and non-surgical therapeutic approaches for GERD.

Table 3 depicts the currently available non-medical therapeutic modalities.

Endoscopic Procedures

Presently, minimally invasive procedures, specifically endoscopic or endoluminal therapies, have developed a unique position in GERD management, and have been proposed as alternative therapeutic strategies for surgical or medical therapy [88]. The main goals of endoscopic therapy are not different from those of medical or surgical treatment. They include, symptom control, improvement in quality of life, healing erosive esophagitis, and providing long term maintenance of both symptoms and healing of esophageal inflammation. Endoscopic approaches are outpatient procedures, less expensive than surgical interventions, relatively safe, can be performed by both surgeons and gastroenterologists, and are very effective. Candidates for endoscopic therapy are those who exhibit typical symptoms of GERD, such as heartburn and regurgitation, have low grade erosive esophagitis (Los Angeles A and B), endoscopy negative with abnormal esophageal acid exposure, a hiatal hernia smaller than 3 cm in size, and at least a partial response to PPI treatment.

Currently, there are three endoscopic techniques that are available in the USA, including the Stretta radiofrequency procedure, transoral incisionless fundoplication (TIF), and Medigus Ultrasonic Surgical Endostapler (MUSE).

Table 3 Comparison of different non-medical techniques to treat GERD

	Endoscopic technique	Heartburn (mean change, 95% CI)	GERD-HRQL (mean change, 95% CI)	Satisfaction (%)	PPI use (cessation of PPI %)	Esophageal acid exposure time (Mean change, 95% CI)	LES pressure (Mean change, 95% CI)
Radiofrequency ablation	Stretta [90••]	Heartburn score − 1.53 (−1.97, −1.09)	−14.60 (−16.48, −12.73)	NA	51	−3.01 (−3.72, −2.30)	+1.73 (−0.29, 3.74)
Endoscopic fundoplication	TIF2.0 (Esophyx) [92, 102]	Total reflux episode −29.07 (−39.17, −18.98)	The pooled RR 2.44 (1.25, 4.79)	69.15	46	−0.34 (−4.02, 3.33)	NA
	GERDx (G-SURG GmbH) [106]	GIQLI from 92.68 to 112.80	NA	NA	47.4	NA	The mean LES resting pressure changed from 20.59 ± 9.85mmH to 30.88 ± 44.46 m-mHg
	MUSE [103]	GERD-HRQL heartburn sub score from 21.9 ± 3.6 to 7.2 ± 7.3	changed from 29.7 ± 6.2 to 9.0 ± 9.1 (73% patient improve)	NA	64.6	changed from 10.9 ± 10.7 to 7.3 ± 5.1	changed from 11.6 ± 8.6 to 12.5 ± 8.0
Endoscopic Gastric Cardia Opening Constriction	ARMS [108]	DeMeester heartburn score changed from 2.7 to 0.3	NA	NA	100	−26	NA
Endoscopic bulking agents injection	Aluvra	NA	NA	NA	NA	NA	NA
LES electrical stimulation	EndoStim [121]	NA	−21	NA	73	−7.1	NA

LES lower esophageal sphincter, *TIF* transoral incisionless fundoplication, *MUSE* medigus ultrasonic surgical endostapler, *ARMS* anti-reflux mucosectomy, *IC* confidence interval, *PPI* proton pump inhibitor, *NA* non-applicable

The Stretta® system delivers radiofrequency energy (RF) to the lower esophageal sphincter and gastric cardia [88]. Increased esophagogastric junction thickness due to modulation of the local musculature and decrease in the frequency of TLESRs are likely responsible for the Stretta® effect on GERD [89].

A recent meta-analysis of 28 studies representing 2468 unique Stretta patients demonstrated that Stretta improved the health-related quality of life score and heartburn standardized score, reduced the percentage of using PPIs, the incidence of erosive esophagitis, and esophageal acid exposure. It was concluded that the Stretta procedure significantly improves GERD-related clinical endpoints, and therefore, should be considered as an alternative to medical or surgical therapy in the management of GERD [90••].

The TIF procedure is an endoscopic technique performed with the EsophyX® Device, to create an anterior full-thickness fundoplication. The procedure is performed under general anesthesia and constructs a valve, 3–5 cm in length and 200 to 300 degrees in circumference. The valve is intended to improve the barrier between the esophagus and the stomach and to significantly reduce gastroesophageal reflux [91].

Multiple studies have evaluated the safety and efficacy of the TIF® procedure, demonstrating that the technique improved symptoms, health-related quality-of-life, PPI utilization, and esophageal acid exposure [92–97].There are five randomized, controlled trials that describe the efficacy of TIF® in patient populations with classic symptoms of GERD, such as heartburn and regurgitation. While several meta-analyses questioned the durability of the procedure, a recent long-term follow-up studies of patients who underwent the TIF procedure showed that its clinical efficacy is durable and very safe [98–100, 101••, 102].

Medigus Ultrasonic Surgical Endostapler (MUSE, Medigus) is an endoscopic stapling device for transoral partial fundoplication. Similar to the EsophyX, the MUSE is designed to create an anterior full-thickness fundoplication using a modified endoscope that incorporates a miniature camera, ultrasound probe, and a stapler on its tip [88] The camera along with the light source allow for direct visualization of the staple site selection, and the ultrasonic range finder helps in assessing the tissue thickness before firing the staples.

There are no randomized controlled trials that evaluated the safety and efficacy of MUSE, and only small non-randomized studies were performed.

In a multicenter, prospective trial that assessed the efficacy of MUSE in 69 patients, almost three-fourth of the patients achieved > 50% improvement in GERD-HRQL, and two-third were no longer using PPI therapy 6 months post procedure [103]. In addition, the mean percent total time pH < 4 significantly decreased from baseline to 6 months post procedure ($p < 0.001$). Another study that was done by Kim et al. analyzed the long-term efficacy and safety data of 37 patients who underwent the MUSE procedure [104]. The proportion of patients who discontinued PPI therapy was 69.4% at 4-year follow-up with a significant improvement in GERD-HRQL. When the MUSE procedure was compared to laparoscopic fundoplication, the MUSE group had a longer procedure time and lengthier stay in the hospital. Additionally, more patients used PPIs and fewer reported improvement in GERD health-related quality of life at 6 months post-procedure than patients who underwent laparoscopic fundoplication [88].

While early studies demonstrated that the MUSE procedure has the potential to position itself as a first-line endoscopic therapy, more research is needed to cement its long-term efficacy in larger number of subjects.

GERDx (*G-SURG GmbH*) a recently launched endoscopic full-thickness plication device that uses hydraulic elements for control requires a slim gastroscope that works as a light source [105].

An interim report of a prospective trial that evaluated the efficacy of the GERDx device in 28 patients with GERD showed an improvement in reflux parameters and quality of life [106]. Weitzendorfer et al. prospectively assessed the efficacy and safety of the procedure in 40 patients with GERD. At 3-month follow-up, the authors demonstrated a significant improvement in reflux symptoms, quality of life, and DeMeester score. However, the procedure failed in 17.5% of the subjects who subsequently underwent laparoscopic fundoplication. Serious adverse events (SAE) were observed in 10% of the patients (4 out of 40), 2 were rated as moderate (hematoma at the GE junction and pneumonia with pleural effusion), and 2 as severe (sutures passed through the liver, and Mallory-Weiss tear at the GE junction). All these adverse events required an intervention [107].

It is still too early to draw any conclusion about the efficacy and safety of the GERDx. However, the preliminary data from less than a handful studies are promising for the future use of the GERDx as another non-medical option for GERD.

Anti-reflux mucosectomy (*ARMS*) is a relatively new endoscopic procedure for gastroesophageal reflux disease (GERD). This technique is consisted of up to 270 degrees endoscopic mucosal resection (EMR) of the gastric cardia around the esophagogastric junction. This results in scar formation leading to narrowing of the gastric cardia opening [108].

The technique was initially described by Inoue et al. in a pilot study that included 10 patients with refractory GERD. The study demonstrated a significant decrease in heartburn and regurgitation scores, flap valve grade (from 3.2 to 1.2, $p < 0.0152$), and PPI use in all patients [108]. Benias et al. performed another pilot study using a novel resection and

plication (RAP) technique, which consisted a semi-circumferential mucosectomy along with full-thickness plication of the lower esophageal sphincter in 10 refractory GERD patients. The authors demonstrated a significant improvement in GERD-HRQL score ($p < 0.0001$, 95% CI 19.3–25.3), and PPI use [109].

The efficacy and safety of ARMS were initially assessed by Hedberg et al. in a retrospective review of their database. Two third of the patients ($N = 19$) reported symptomatic improvement and discontinuation of PPI treatment. Three patients (16%) experienced dysphagia which was resolved by endoscopic balloon dilatation. Third (6 of 19) of the procedures failed, and three of the patients underwent additional anti-reflux surgery [110].

Anti-reflux mucosectomy (ARMS) could also be done by using band ligation device (ARMS-b) to perform a piecemeal mucosectomy of three-quarter of the EGJ circumference. This technique was described in a case report of a patient with refractory GERD. At a 1-year follow-up, the patient did not report symptoms recurrence, and there was no evidence of reflux on pH monitoring [111]. Saleem et al. investigated the efficacy and safety of the ARMS procedure using band ligation (ARMS-b) in a randomized trial that included 150 patients with refractory GERD. Three to four rubber bands were applied at the level of the esophagogastric junction during the one or two endoscopic sessions. There was a significant improvement in GERD-HRQL score in the banding group as compared to the PPI group. No major adverse events were reported at 1-year follow-up [112]. Hu et al. developed another method of ARMS called peroral endoscopic cardial constriction (PECC) which is based on two band ligations placed at the cardia and fixation of the ligations with clips. Thirteen GERD patients, who were enrolled and underwent the procedure, reported a significant improvement in GERD-HRQOL score and esophageal acid exposure [113].

A different way of performing ARMS is the cap-assisted endoscopic mucosal resection method (ARMS-C). The technique demonstrated a significant decrease in GERD symptoms score, DeMeester score, and esophageal acid exposure time. Except two balloon dilatations of an esophageal stricture, there were no serious adverse events [114].

Aluvra is a novel injectable bulking agent for the treatment of GERD that is currently evaluated by a prospective, double-blind, randomized controlled trial. The safety and efficacy of this bulking agent for the treatment of gastroesophageal reflux disease will be assessed in 100 patients. The trial is scheduled to be completed in 2020. [NCT03090607].

Surgery

Recently, electrical stimulation of the LES was introduced as an additional alternative technique for the treatment of GERD. In this technique, an implantable pulse generator device with 2 stitch electrodes is placed subcutaneously in the anterior abdominal wall, and the electrodes are anchored laparoscopically in the lower esophageal sphincter [115].

EndoStim (EndoStim BV, The Hague) is an electrical stimulation technique that has been shown to increase LES resting pressure in animal models [116–118]. Human studies, however, focused primarily on patients with erosive esophagitis who are on PPI treatment, and have low resting LES pressure. The authors demonstrated that short-term electrical stimulation of the LES improve LES resting pressure, esophageal acid exposure, GERD-HRQL, and PPI consumption without affecting esophageal peristalsis amplitude or LES relaxation [85, 119, 120].

Long-term follow-up of up to 3-years post EndoStim placement revealed durability of the original therapeutic effect [121]. Furthermore, EndoStim technique showed similar clinical outcomes in patients with refractory GERD [122]. The EndoStim appears to be a reasonable option for patients post-laparoscopic sleeve gastrectomy or post-POEM that developed de novo or worsening preexisting GERD not controlled with maximum PPI therapy [123, 124]. Additionally, the EndoStim may be a promising option for PPI-refractory GERD patients particularly for those with severe ineffective esophageal motility (IEM) [125]. Recently, the EndoStim multi-center trial in the USA was discontinued due to lack of efficacy.

Although electrical stimulation of the LES proved to be safe and effective in short and long-term studies in humans, this technique still requires surgical intervention under general anesthesia. Using endoscopic approach, the studies in canine models have shown a significant increase in resting LES pressure [126–128]. Hajer et al. used a pig model to investigate a newly developed miniature implantable device without a battery to treat GERD through electrical stimulation of the LES. The device was implanted endoscopically in the submucosa by using the same endoscopic submucosal tunneling method that is currently used for POEM. The safety of this technique is similar to POEM. However, this procedure does not require myotomy [129]. The authors plan to confirm manometrically the LES stimulation effect in a living pig.

Conclusions

The PPIs remain the mainstay of therapy for GERD. However, the recent introduction of several new compounds from the P-

CAB class of drugs may offer resolution to several areas of unmet needs in GERD, such as severe erosive esophagitis, refractory GERD, and post-prandial heartburn. The mucosal protectants is another promising class of drugs with possible role as an add on to PPI treatment or as a sole therapy. Of the new prokinetics, prucalopride appears to have a general gastrointestinal promotility effect, including the esophagus. Development of specific pain modulators for the esophagus remains desirable. Presently, endoscopic therapy for GERD is in its best position, because more patients are seeking an alternative to PPI treatment, and less are interested in a surgical option for their GERD.

Compliance with Ethical Standards

Conflict of Interest FS and YK declares that they have no conflict of interests.

RF is an advisor of Ironwood, Takeda, and Daewoong; is a speaker of Astrazeneca, Takeda, and Eisai; and performs research for Ironwood.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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