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Current Scenario of Pharmacological Approaches for Gastroesophageal Reflux Disease

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Abstract: Back ground: Gastro Esophageal Reflux Disease (GERD) is a common disorder, affecting approximately 10-20% of the western population and often has a debilitating effect on the daily lives of patients. **Result:** GERD can be described as any symptomatic condition or histopathologic alternation resulting from episodes of gastroesophageal reflux. Transient relaxation of the lower oesophageal sphincter is believed to be the primary mechanism of the disease although the underlying cause remains uncertain. GERD usually manifests as heartburn, regurgitation, or dysphagia and predisposes to development of esophagitis, stricture, Barrett's metaplasia, esophageal adenocarcinoma. The various agents currently used for treatment of GERD include proton pump inhibitors, antacids, H2-blockers, mucoprotective substances and prokinetic agents. **Conclusion:** This review gives an overview of the pharmacological management of GERD and summarizes the state of the art with these agents.

Key words: Gastroesophageal reflux disease, GERD pharmacotherapies, PPIs, prokinetic agents, P-CABs

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common and often lifelong problem that is expensive to manage. The annual direct cost for managing the disease is estimated to be more than $9 billion dollars in the USA(Sandler *et al*., 2002). With its huge disease burden, it has considerable clinical and economic implications for the practicing physician. Although absence of a standardized definition of GERD hampered an accurate estimates of prevalence, a recent systematic review, based on the occurrence of typical reflux symptoms (at least once weekly), reported a prevalence of GERD ranging from less than 5% in Asia to 10-20% in the Western world (Dent *et al*., 2005). GERD is associated with a wide range of symptoms, the most common are heartburn and regurgitation. Additional GERD related symptoms referable to upper GI tract are epigastric pain, angina-like chest pain, epigastric burning, dysphagia, nausea and extra-esophageal symptoms such as hoarseness, globus sensation, cough and wheezing. In view of the large clinical spectrum and lack of specific diagnostic test, it is difficult to define GERD. However recently, based on a combination of disease characteristics, GERD was defined as applying to individuals with reflux of gastric contents into the oesophagus causing symptoms sufficient to reduce quality of life and/or esophageal injury (DeVault and Castell, 2005).

The pathophysiology of GERD involves an imbalance between aggressive factors related to the stomach and distal Gastro Intestinal (GI) tract and defensive mechanisms meant to protect the esophagus (Fig.1). Despite of the fact that most of the signs and symptoms of GERD are produced mainly due to the effects of acid and pepsin, the traditional dogma defined GERD as a manifestation of a motility disorder. In particular, the esophageal antireflux mechanism consisting of the Lower Esophageal Sphincter (LES) and the crural diaphragm are the key defence mechanisms against GERD and dysfunctions involving these parts of the GI tract account for virtually all reflux episodes in healthy individuals and up to 80% of episodes in patients with GERD. Although the apparent causes of incompetent LES functions and frequent Transient Lower Esophageal Sphincter Relaxation (TLESRs) episodes in GERD patients is not clear, but gastrointestinal dysmotility (causing delayed gastric emptying or impaired fundic relaxation), diet, obesity, factors such as oestrogen (e.g. during pregnancy) and medications all are considered to be involved.

GERD can be subdivided into Erosive Esophagitis (EE) and Non-Erosive Reflux Disease (NERD). Patients with NERD have no endoscopic lesions in the esophagus, but have typical reflux symptoms (Moayyedi and Talley, 2006). Again, it is not clear why some patients have NERD while others with comparable esophageal acid exposure

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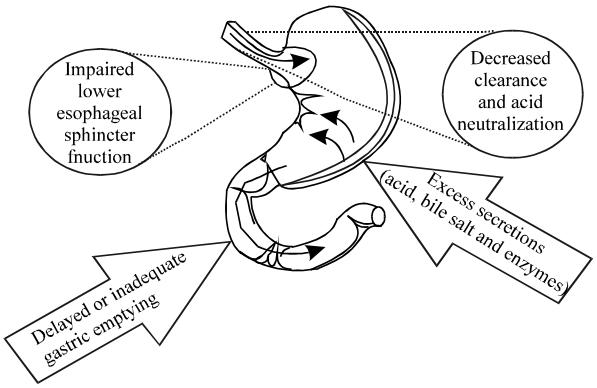

Fig. 1: Possible pathophysiological mechanisms of Gastro-Esophageal Reflux Disease (GERD)

develop esophageal erosions, ulceration, strictures or Barrett's epithelium (a precancerous condition which can lead to esophageal adenocarcinoma). It could be that patients with esophageal lesions have week tissue resistance mechanisms (related to esophageal luminal clearance of reflexed gastric contents), epithelial bicarbonate secretion or salivary bicarbonate production compared to patients with NERD that most likely have strong esophageal sensitivity to luminal contents.

As a consequence of the multifactorial aetiology of esophageal lesions and symptoms, there are several potential therapeutic targets that can be considered. Treatment options available for GERD range from Over-The-Counter (OTC) antacids to Proton Pump Inhibitors (PPIs) and anti-reflux endoscopic procedures and surgery. Present article reviews each of the pharmacotherapeutic options including new developments in proton pump inhibitor isomers, potassium competitive acid blockers and endoscopic therapy for gastroesophageal reflux disease.

AGENTS TARGETING GASTRIC ACID SECRETIONS

Proton pump inhibitors: Proton Pump Inhibitors (PPIs) are the most effective pharmacologic agents for the treatment of GERD. There are currently 5 PPIs available: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole, of which only omeprazole is available as an OTC. PPIs are prodrug which is converted into sulphonamide by an actively secreting gastric parietal cell. The trapped sulphonamide then binds irreversibly to the H+-K+-ATPase and blocks the secretion of protons. Because they block the final step in acid production, the PPI are effective in acid suppression regardless of other stimulating factors. In typical doses, these drugs diminish

Table 1: New isomeric PPIs and comparison of their therapeutic and healing efficacy with parent PPIs

Isomeric PPIs	Parent racemates	Symptom relief compared to parent PPIs	Efficacy healing compared to parent PPIs
Esomeprazole	Omeprazole	Better	Better
S-pantoprazole	Pantoprazole	Better	Equally effective
Dexrabeprazole	Rebeprazole	Better	Better
Dexlansoprazole	Lansoprazole	Better	Better

the daily production of acid (basal and stimulated by 80-90%) (Wallace and Sharkey, 2011). There are now many studies and meta-analyses indicating that PPI therapy results in the best symptom control in patients with NERD or erosive esophagitis and erosive esophagitis healing (Armstrong *et al*., 2005; Chiba *et al*., 1997; Van Pinxteren *et al*., 2003).

Although PPIs have a prolonged effect, their effects are limited to some extent; clinically, their onset is relatively slow and, because they are effective only in actively secreting parietal cells, acid can be secreted from cells that were inactive during the relatively short period when they were exposed to PPIs in the plasma. In addition, acid secretion returns as new proton pumps are synthesized and inserted into the secretory canalicular membrane after clearance of the sulphonamide from the secretory canaliculus.

Apart from these limitations, Long-term use of PPIs has potential areas of concern which includes hypergastrinemia and rebound, hypersecretion following drug withdrawal, high ulcer relapses, tolerance and various drug interactions (Wallace and Sharkey, 2011). However recent review of the potential gastrointestinal effects of long-term acid suppression with PPI showed that these agents rarely, if ever, produce adverse events (Klinkenberg-Knol *et al*., 2000).

Now a days racemic mixture of S and R isomers of proton pump are gaining recognition. These isomers of proton pump inhibitors show superior therapeutic efficacy and have better metabolic and pharmacokinetic profile compared to their parent racemates (Table 1).

Tenaprazole (Tu-199), a novel chemical compound belonging to the proton pump inhibitor class is also undergoing clinical trials. Tu-199 have substantially prolonged half-life (7 h) and few reports indicates that it achieve significantly better control of nocturnal acidity than esomeprazole (Galmiche *et al*., 2005).

Histamine h2-receptor antagonists: Gastric acid secretion by parietal cells of the gastric mucosa has a complex control mechanism. The endogenous mediators viz. acetylcholine, gastrin and histamine all are involve. These mediators act through their own receptors and trigger unique series of biochemical events within the parietal cell

which ultimately stimulate gastric acid secretion. The H2 receptor antagonists inhibit acid production by reversible competing with histamine for binding to H2 receptors on the basolateral membrane of parietal cells. All four of the H2RAs: Cimetidine, ranitidine, famotidine and nizatidine, which differ mainly in their pharmacokinetics and propensity to cause drug interactions, are available as prescription and OTC formulation for oral administration. These drugs are less potent than PPIs but still suppress 24 h gastric acid secretion by ˜70%. The H2 receptor anatagonist predominantly inhibits basal acid secretion, which accounts for their efficacy in suppressing nocturnal acid secretion. These are approved for acute treatment of episodic heartburn, or for prophylaxis before an activity that may potentially result in reflux symptoms (Heavy meal or exercise in some patients). H2RA therapy is generally safe, the most commonly reported adverse events were diarrhea and headache. Cimetidine inhibits cytochrome P450 and can slow metabolism of several drugs (for example, warfarin, phenytoin, diazepam), thus sometimes resulting in serious adverse clinical effects.10 Most H2RAs cross the placenta thus they are advised to use with caution during pregnancy. The rapid development of pharmacological tolerance (within 7-14 days) is a further disadvantage of H2RAs and the loss of gastric acid secretion suppression obtained with these agents may partially explain their unsatisfactory use in patients with GERD (Wallace and Sharkey, 2011).

Antacids and alginates: The most common agents used by patients with GERD symptoms are antacids because of their easy availability and rapid symptom relief. Antacids, usually are weak bases of aluminum-and/or magnesium that act locally to buffer the acidity of the gastric and esophageal contents, providing quick relief. Antacids also lessen peptic activity since pepsin is inactive at pH 4.0. Because of rapid esophageal clearance, however, antacids provide only short-term relief of the symptoms of GERD and have no role in controlling nocturnal acid secretion, healing esophagitis, or preventing complications (Fass *et al*., 1997). Alginate-based raft-forming formulations are used for the symptomatic treatment of heartburn and esophagitis and appear to act by a unique mechanism which differs from that of traditional antacids. In the presence of gastric acid, alginates precipitate, forming a gel. Alginate-based raft-forming formulations usually contain sodium or potassium bicarbonate and in the presence of gastric acid, the bicarbonate is converted to carbon dioxide which becomes entrapped within the gel precipitate, converting it in to a foam which floats on the surface of the gastric contents, much like a raft on water (Mandel *et al*., 2000). The viscous, pH-neutral, protective barrier floats on the top of the gastric contents, preventing acid contact with the esophagus during an episode of reflux. An alginic acid/antacid combination that prevents contact of acid refluxate with esophageal mucosa provides better symptom relief than antacids and may maintain remission in patients whose mild to moderate esophagitis has healed with histamine 2 receptor (H2) blockers or Proton Pump Inhibitor (PPI) therapy. They are also useful in special populations, such as pregnant patients, where acid suppressive medications may not be the best option.

DRUGS TARGETING MUCOSAL PROTECTION

There has been little research into the role of mucosal protectants in recent years despite early reports of the potential benefit of prostaglandin analogues and the results of a large meta-analysis which suggested that sucralfate is beneficial in the healing of erosive esophagitis (Chiba *et al*., 1997). The role of prostaglandin analogues is likely to be contentious as there is now some support for the role of cyclooxygenase-2 inhibitors in chemoprevention therapy for Barrett's esophagus (Hur *et al*., 2004).

Sucralfate: Sucralfate, a mucosal protective agent prevent mucosal injury, inflammation and heals existing ulcers by improving the mucosal protection mechanism. Sucralfate consist of the octasulfate of sucrose to which AL(OH)3 has been added. In an acid environment (pH<4), it undergoes extensive crosslinking to produce a viscous, sticky polymer that adheres to epithelial cells and ulcer crater for upto 6 h after a single dose. In addition to inhibiting hydrolysis of mucosal protein by pepsin, sucralfate may have additional cytoprotective effects, including stimulation of local production of PGE_2 and epidermal growth factor. Sucralfate also binds bile salts, thus some clinicians use sucralfate to treat individuals with the syndrome of biliary esophagitis. Sucralfate provides similar level of symptomatic relief to that of H2RAs; however, studies evaluating sucralfate in the healing of GERD have produced inconsistent results, with reported healing rates varying from 17-67% (Chiba *et al*., 1997; Tytgat, 1987). A systemic review evaluated the effectiveness in healing erosive esophagitis of mucosal protective agents compared with H2RA therapy alone or H2RAs combined with mucosal protective agents did not show statistically significant benefit of the combination therapy compared to sucralfate monotherapy in healing of peptic reflux esophagitis (Khan *et al*., 2007). Mucosal protective agents are inferior to antacid/ alginates, H2RAs and PPIs in the treatment of

erosive esophagitis and in relieving symptoms of GERD. The efficacy of mucosal protective agents in healing esophagitis has not been documented in systemic database review.

AGENTS TARGETING LES MOTILITY AND TLESRS

Although at present antisecretory agents are the mainstay of pharmacological treatment, drugs targeting motility may have a role in the treatment of gastro-oesophageal reflux as defects in esophagogastric motility (LES incompetence, poor esophageal clearance and delayed gastric emptying) are central to the pathogenesis of GERD. If these defects could be corrected then GERD would be controlled, making suppression of normal amounts of gastric acid unnecessary.

Serotonin receptor ligands: Among serotonin receptor ligands, only serotonin 5-HT4-receptor agonists and 5-HT3-receptor antagonists have been demonstrated to produce relief of symptoms. Cisapride is a 5-HT 4 receptor agonist with moderate 5-HT 3-receptor antagonist properties, whose beneficial effect on oesophageal motility in GERD is still a matter of discussion. Several studies supported the use of cisapride in GERD for its ability to favour oesophageal peristalsis (and, therefore, to enhance acid clearance from the esophagus), to increase LES pressure and to improve gastric emptying (De Ponti and Malagelada, 1998). However, cisapride have not proved to be particularly effective in routine practice and have failed to compete with the superior efficacy of PPIs, especially among patients with severe reflux oesophagitis (De Caestecker, 2002) and in terms of health-related quality of life benefits (Van Pinxteren *et al*., 2006). In addition, some of the 5-HT4 receptor agonists have safety liabilities and have been withdrawn from the market because of serious cardiovascular adverse events. For example, cisapride was withdrawn from the market in year 2000 after an association with serious cardiac arrhythmias became apparent. In March 2007, US marketing and sales of tegaserod (Novartis), a 5-HT4 receptor agonist used in the treatment of constipation and irritable bowel syndrome that was being developed as a potential new treatment for GERD and dyspepsia, was withdrawn in response to a significantly increased risk of cardiovascular adverse events. Despite the safety problems that have limited the usefulness of older prokinetics, one agent is still undergoing development: ATI-7505 (ARYxTherapeutics), a cisapride analogue that is undergoing phase II clinical development for GERD (ARYxTherapeutics, 2009). To date, no cardiac safety problems have been reported in>600 patients exposed to ATI-7505 which significantly improved heartburn symptoms in a placebo controlled phase II study in GERD patients (ARYxTherapeutics, 2008). The clinical development of Pumosetrag (DDP773, Dynogen Pharmaceuticals), a selective partial 5-HT3 receptor agonist with gastrokinetic activity that demonstrated reflux-reducing efficacy in healthy volunteers (Choung *et al*., 2008) for nocturnal GERD, was ceased due to company bankruptcy in February 2009.

Muscarinic-receptor agents: Several lines of evidence are consistent with the notion that, in humans, acetylcholine released by post-ganglionic cholinergic nerves contributes to the regulation of peristalsis in the smooth muscle portion of the oesophageal body and to LES tone (Dodds *et al*., 1981). Bethanechol is a direct-acting muscarinic receptor agent that acts by stimulating the parasympathetic nervous system to release acetylcholine. It has been shown to increase LES pressure and improve esophageal peristaltic clearing(Maton, 2003). Bethanechol has variable systemic absorption, with onset of action between 30 to 90 min after oral ingestion and duration of action up to 6 h. It should be taken 1 h before meals. However the frequent central nervous system side effects have appropriately decreased the regular use of bethanecol in GERD patients.

D2 receptor antagonist: Dopamine is an important mediator of gastrointestinal secretion, absorption and motility. Metoclopramide, a dopaminergic antagonist significantly increases basal LES pressure and decreases reflux episodes, aids in esophageal peristalsis and speeds gastric emptying commonly during the third and fourth h postprandially (Durazo and Valenzuela, 1993). However, the clinical efficacy of this drug as monotherapy for GERD has not been consistently proved and the side-effect profile of metoclopramide makes the drug unattractive for regular use (Hixson *et al*., 1992). The drug's action is mediated through blockade of the central and gut dopaminergic receptors and the release of acetylcholine from postganglionic nerves in the myenteric plexus. The ability of metoclopramide to cross the blood-brain barrier has resulted in various side effects such as extrapyramidal movement disorders, restlessness, confusion, insomnia and drowsiness. Domperidone is another dopamine receptor blocker but unlike metoclopramide does no easily cross the blood-brain barrier and therefore has little central nervous system effects. It has peripheral dopamine receptor blocking properties and increases esophageal peristalsis and LES pressure, increases gastric motility and peristalsis; therefore, facilitating gastric emptying and decreasing small bowel transit time (Barone, 1999).

Itopride is another recent prokinetic that has activity as a dopamine D2 receptor antagonist and a cholinesterase inhibitor; on the basis of its acceleration of gastric emptying and modulation of gastric sensorimotor function, it has potential for the management of functional dyspepsia and, in a pilot, dose-ranging study, there was evidence that the higher of the two doses (itopride 300 mg daily versus 150 mg daily) reduced esophageal acid exposure in patients with mild to moderate GERD (Kim *et al*., 2005).

Gaba-b receptor antagonist: GABA is a fundamental inhibitory neurotransmitter in the central and peripheral nervous system. GABA exerts its inhibitory effect on LES by preventing neurotransmitter release in the vagal pathways controlling LES relaxation. Baclofen, a GABA-B-receptor agonist have has shown potential in clinical trials relevant to GERD at a single dose of 40 mg (Cange *et al*., 2002). The mechanism appear to be suppression of transient LES relaxation. Interestingly, baclofen can decrease the rate of TLESRs and increase the basal LES pressure without altering the meal-induced fundus accommodation (Lee *et al*., 2003). In one study of 16 patients with continued reflux symptoms while on PPI therapy, the addition of baclofen 20 mg thrice daily significantly decreased the cumulative severity score for a range of reflux symptoms (Zhang *et al*., 2002). However, despite these positive findings, the therapeutic utility of baclofen is limited by central adverse effects along with a requirement for frequent dosing (three to four times daily) due to a short half-life (Vela *et al*., 2003). The attempts to overcome the tolerability issues encountered with baclofen have resulted in the discovery of novel compounds such as arbaclofen placarbil (XP19986, XenoPort), lesogaberan (AZD3355, AstraZeneca) and ADX10059 (Addex Pharmaceuticals). Arbaclofen placarbil which is a R-isomer of baclofen and lesogaberan are currently undergoing development for the treatment of GERD and have shown promising efficacy in proof-of-concept clinical trials. However, the development of ADX10059 for chronic conditions has recently been stopped due to the of potential drug-induced hepatotoxicity.

Cholecystokinin receptor antagonists: Gonzalez *et al*. (2000) have shown that CCK exerts a direct excitatory effect on human isolated LES circular muscle by activating CCK1 receptors, a response antagonised by loxiglumide (a selective CCK1-receptor antagonist) and lintitript (SR-27897; a nonselective CCK-receptor antagonist), but not by selective CCK2-receptor antagonists. A recent study carried out in healthy volunteers and patients with GERD has shown that loxiglumide attenuated TLESRs caused by meal ingestion, although its effect on gastro-oesophageal acid reflux was quite modest (Trudgill *et al*., 2001). Inhibition of gall bladder emptying associated with gall stone formation is a potential effect of CCK antagonists, but long-term clinical studies have excluded this effect for dexloxiglumide, the active enantiomer of the parent racemic compound loxiglumide (D'Amato *et al*., 2001).

Motilin receptor agonist: The antibiotic erythromycin, which undergoes an acid-catalysed rearrangement in the stomach to form a motilin agonist and is sometimes used off-label to treat GERD and its derivatives with no antibacterial activity but preserved or even higher motilin-like properties so-called motilides, such as alemcinal (ABT-229; Abbott Laboratories) and mitemcinal (GM-611; Chugai) all have limited utility for GERD (Tonini *et al*., 2004).

MISCELLANEOUS AGENTS

P-CABs: Potassium-competitive acid blockers (P-CABs) represent a new class of drugs acting through a reversible binding mechanism different from the PPIs. There are several compounds (soraprazan, AZD0865, revaprazan), known initially as 'reversible' PPIs and categorized now as potassium-competitive acid blockers (P-CABs), which bind to the proton pump at or near the site of the potassium channel (Mossner and Caca, 2005; Vakil, 2004). P-CAB binding to the proton pump is competitive and reversible and these compounds inhibit acid secretion rapidly, within 30 min of administration; whereas classical PPIs need several days to reach their steady-state effect. Moreover, P-CABs are active in the absence of stimulated acid secretion and their effect is rapidly reversible. Therefore, P-CABs generated considerable research interest as potential new therapies for GERD. However, recent study with AZD0865 showed that despite of pronounced effects on acid secretions, marginal effects were observed on healing rates and symptoms control compared to PPI (Dent *et al*., 2008; Kahrilas *et al*., 2007). Therefore, with the exception of TAK-438 (Takeda) and revaprazan (Yuhan), most pharmaceutical companies have discontinued clinical development of their P-CAB compounds. Clinical data for both agents in the setting of GERD are currently lacking, further research will show whether these two compounds are able to overcome the disappointing results seen with AZD0865.

ENDOSCOPIC THERAPY

GERD is a chronic condition with a high tendency toward relapse when medical treatment is discontinued Acid suppression can be effective in most patients with

GERD, but long-term therapy is expensive and the treatment does not address the main abnormality in reflux disease: the abnormal relaxation of the lower oesophageal sphincter. Recently, endoluminal therapies have arisen as an alternative to conventional antireflux therapy and can be divided into three approaches: (1) endoscopic suturing devices for the lower oesophageal sphincter; (2) the endoscopic application of radio-frequency to the lower oesophagus; and (3) the injection of bulking agents into the muscle layer of the distal oesophagus. These therapies have been offered to patients who are averse to the long-term complications of prolonged acid suppression therapy, who are responders to medical treatment and are seeking an alternative to surgery (Jeansonne *et al*., 2009).

The aim of endoscopic suturing devices is to insert three stitches circumferentially or longitudinally in the gastric cardia to plicate and strengthen the lower oesophageal sphincter. Temperature-controlled radio-frequency energy delivered to the cardia could reduce the frequency of lower oesophageal sphincter relaxations. The mechanism by which this occurs is unclear. The procedure involves positioning a probe at the gastro-oesophageal junction and the application of radiofrequency to eight circumferential points in the cardia which takes 40–60 min. The third approach is to inject an insoluble copolymer (e.g, polyethylene and polyvinyl alcohol) into the muscle layer of the oesophagus. This results in a polymer precipitating in the muscle layer.

All of the endoscopic techniques seem to produce an improvement in reflux symptoms, although significant changes in LES pressure have not been documented and less than 35% of patients have been demonstrated to have normalization of their intra-esophageal acid exposure by ambulatory pH testing (DeVault and Castell, 2005). Unresolved issues remain with the endoluminal therapies, including long-term durability, safety and efficacy. Further investigations are needed.

CONCLUSION

Gastro Esophageal Reflux Disease (GERD) is one of the most common diagnoses in daily practice. To date TLERS (75%) and decreased LES (20%) are believed to be the major motility disorders underlying GERD. The cardinal symptoms of GERD are heartburn and regurgitation. Available pharmacotherapeutic options for GERD range from OTC antacids and alginates, H2RAs, mucosal protective agents, prokinetics and drugs that enhance LES pressure. Only H2RAs and PPIs have been found to be effective and safe in the treatment of erosive esophagitis and in long-term maintenance therapy. Prokinetic agents can be helpful in certain individuals with GERD symptoms while on maximal dosing of PPI therapy; however, the associated side effects limit their usefulness in the disease management. Various endoscopic techniques had been developed as alternatives to surgery, in patients who are averse to the long-term complications of prolonged acid suppression therapy. However, Further studies are warranted to assess the safety and long-term advantages of these endoscopic therapies.

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