Review Article

New Pharmacological Therapies for Treatment of Gastroesophageal Reflux Disease

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a chronic, relapsing disorder characterized by recurrent symptoms of acid reflux with esophageal injury. It rarely resolves spontaneously, and it is associated with frequent recurrences. It has adverse impact on quality of life. A variety of medications have been used in GERD treatment, and acid suppression therapy is the mainstay of treatment for GERD. Although proton pump inhibitor is the most potent acid suppressant and provides good efficacy in esophagitis healing and symptom relief, about one-third of patients with GERD still have persistent symptoms with poor response to standard dose proton pump inhibitors (PPI). These are generally well tolerated but there are associated with minor side effects such as headache, diarrhea, and abdominal pain. Newer formulations of PPI which have faster and longer duration of action and potassium-competitive acid blocker, a newer acid suppressant, are also in developing stages. Transient lower oesophageal sphincter relaxation (TLESR) is an important factor behind the occurrence of reflux, and preclinical studies have identified gamma aminobutyric acid (GABA) type B receptor ($GABA_B$) agonists and metabotropic glutamate receptor 5 (mG1uR5) modulators as candidate drugs for modifying TLESR. Another novel therapeutic agent has focused on the underlying mechanisms of GERD, such as motility disorder, mucosal protection, and esophageal hypersensitivity are also under clinical trials.

Keywords: GERD, PPI, gastric acid, esophagitis

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as "a condition which develops when the reflux of gastric contents into the esophagus causes troublesome symptoms (i.e., at least two heartburn episodes/week) and/or complications"[1].GERD is the most common digestive disease in the Western world, with an estimated prevalence of 10 – 20% [2].With respect to the esophagus, the spectrum of injury includes esophagitis, stricture, Barrett's esophagus, and adenocarcinoma. There were about 8,000 incident cases of esophageal adenocarcinoma in the United States in 2010 (half of all esophageal cancers); it is estimated that this disease burden has increased two- to six fold in the last 20 years [3].

The normal antireflux mechanisms consist of the lower esophageal sphincter (LES), the crural diaphragm, and the anatomical location of the gastroesophageal junction below the diaphragmatic hiatus. Reflux occurs only when the gradient of pressure between the LES and the stomach is lost. It can be caused by a sustained or transient decrease in LES tone. A sustained hypotension of the LES may be due to muscle weakness that is often without apparent cause. Secondary causes of sustained LES incompetence include scleroderma-like diseases, myopathy

associated with chronic intestinal pseudo-obstruction, pregnancy, smoking, anticholinergic drugs, smooth muscle relaxants (β- adrenergic agents, aminophylline, nitrates, calcium channel blockers, and phosphodiesterase inhibitors), surgical damage to the LES, and esophagitis [3]. Reflux mainly occurs during prolonged relaxations of the lower esophageal sphincter (LES) not related to swallowing, now referred to as transient lower esophageal sphincter relaxations (TLESRs) [4]. Such relaxations are a vago-vagal reflex mediated motor pattern generated in the brain stem and triggered by distension of the stomach with free air or ingestion of a meal [5]. Increased episodes of TLESRs are associated with GERD. Apart from incompetent barriers, gastric contents are most likely to reflux when gastric volume is increased (after meals, in pyloric obstruction, in gastric stasis, during acid hypersecretion states), when gastric contents are near the gastroesophageal junction (in recumbency, bending down, hiatal hernia), and when gastric pressure is increased (obesity, pregnancy, ascites, tight clothes). Incompetence of the diaphragmatic crural muscle, which surrounds the esophageal hiatus in the diaphragm and functions as an external LES, also predisposes to GERD. Obesity is a risk factor for GERD. Acid refluxed into the esophagus is neutralized by saliva. Thus, impaired salivary secretion also increases esophageal exposure time. If the refluxed material extends to the cervical esophagus and crosses the upper sphincter, it can enter the pharynx, larynx, and trachea. Though the refluxed gastric juice is harmful to the esophageal epithelium, gastric acid hypersecretion is usually not a dominant factor in the development of esophagitis. An obvious exception is with Zollinger-Ellison syndrome, which is associated with severe esophagitis in about 50% of patients. Pepsin, bile, and pancreatic enzymes within gastric secretions can also injure the esophageal epithelium, but their noxious properties are either lessened in an acidic environment or dependent on acidity for activation. Bile is more dangerous because it persists in refluxate despite acid-suppressing medications. Bile can transverse the cell membrane, imparting severe cellular injury in a weakly acidic environment, and has also been invoked as a cofactor in the pathogenesis of Barrett's metaplasia and adenocarcinoma. Hence, the causticity of gastric refluxate extends beyond hydrochloric acid.

Management

The goals of treatment are to provide symptom relief, heal erosive esophagitis, and prevent complications. Treatment approach is according to the level of severity (**Table 1**). The options include lifestyle modifications, medical and non-medical (Antireflux surgery) management. Lifestyle modifications include reducing weight, sleeping with the head of the bed elevated by about 4–6 inches with blocks, and elimination of factors that increase abdominal pressure. Patients should not smoke and should avoid consuming fatty foods, coffee, chocolate, alcohol, mint, orange juice, and certain medications (such as anticholinergic drugs, calcium channel blockers, and other smooth-muscle relaxants). They should also avoid ingesting large quantities of fluids with meals.

Medical need for new drugs for GERD

Due to high prevalence of GERD the medical costs involved seems to be enormous. The prevalence of both typical and atypical GERD has significantly risen over the last decade, increasing the demand for adequate GERD treatment. Though proton pump inhibitors have been extremely effective for both healing of erosive esophagitis as well as controlling heartburn symptoms for the majority of GERD patients, there is still a substantial subclass of patients (up to 40%) who do not completely respond symptomatically to a standard dose of PPIs. Refractory gastro-esophageal reflux disease (GERD), defined as persistent symptoms despite proton pump inhibitor (PPI) therapy, is an increasingly prevalent condition and is becoming a major challenge for the clinician. The specific explanation for PPI treatment failure is not clearly known. Possible pathophysiologic mechanisms include: transient lower esophageal sphincter relaxations (TLESRs), sensitivity to weakly acidic and/or alkaline reflux, large volume of reflux, and esophageal hypersensitivity [6].

Table 1: Therapeutic approach in GERD patients according to the level of severity as follows [7].

Stage	Criteria	Medical management
I	Sporadic uncomplicated heartburn, often in setting of known precipitating factor. Often not the chief complaint. Less than 2-3 episodes per week. No additional symptoms.	Lifestyle modifications Antacids and/or H_2 receptor antagonists as needed
II	Frequent symptoms with or without esophagitis. Greater than 2-3 episodes per week.	Proton pump inhibitors more effective than H_2 receptor antagonists
III	Chronic unrelenting symptoms; immediate relapse off therapy. Esophageal complications (eg: stricture, Barret's metaplasia).	Proton pump inhibitors either once or twice daily

Erosive esophagitis healing is one important trial endpoint, and a substantial proportion of patients do not heal after standard doses of PPIs for 8 weeks. Nonresponse of erosive esophagitis increases with severity of erosive esophagitis grading. An intragastric pH of at least 4.0 maintained for 16 h is generally considered the target to promote healing of erosive esophagitis with antisecretory drugs [8]. Most patients will experience reflux after midnight, when the supine time is associated with more reflux events [9]. About 60% to 80% of patients have persistent gastric acidity at night despite twice-daily PPIs. PPIs only change the chemical composition of the refluxate. Number of reflux events remains unchanged as they do not have any effect on LES tone. With their prolonged use, there is an increased risk of gynaecomastia, atrophic gastritis, vitamin B12 deficiency, enteric infections and hip fracture [10]. In clinical practice, low compliance or failure to properly time intake of medication (30 min before the meal) certainly contribute to PPI failure. This implies that good instruction and education of the patient is indeed important and should be the first approach in these cases. In patients optimally taking their medication, doubling of the standard dose or switching to another PPI, or even addition of a H_2 receptor antagonist before the night may increase healing (by 6%) or symptom improvement (by 22 – 26%) [11]. In spite of this, a large proportion of patients remains as partial or non-responders and require further or alternative treatment, especially in non-erosive reflux disease (NERD) patients. Recent studies emphasize that non-acidic reflux may also contribute to symptom generation [12]. There may also be a ceiling effect for the use of PPI therapy. Thus there is a continuous need for new drugs for the better management of GERD patients. New inhibitors of the proton pump with a longer half-life, acting faster and longer, have been developed, including potassium-competitive acid blockers. There is also a need for new therapeutic strategies reducing not only acid but also non-acidic reflux. Newer drugs under this class are known as 'reflux inhibitors.' Other newer drugs are being developed with the aim of reducing increased esophageal perception. This review aims at reviewing the upcoming agents under both acid suppressing and non-acid suppressing strategies for the pharmacological management of GERD.

Recent advances in acid suppression strategy

With respect to acid suppression, PPIs are superior to H_2RA or antacids in reducing gastric acid secretion, esophageal acid exposure and associated symptoms and in healing of mucosal damage. Currently available PPIs like omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole, are equally effective, with some slight superiority for esomeprazole in patients with severe esophagitis [13]. Based on the assumption that better reduction in acid secretion leads

to better clinical outcome, several efforts have been made to develop newer drugs or formulations, which are intended to provide faster, better and more prolonged suppression of acid secretion.

Newer acid suppressing agents can be studied under three headings

1. New formulations of existing PPIs
2. New PPIs
3. Drugs with novel mechanism of acid suppression: potassium-competitive acid blockers (P-CABs)

New formulations of existing PPIs

By optimizing the PPI pharmacokinetics and extending the period of exposure to effective concentrations, improved acid suppression can be obtained. New formulations with prolonged delivery of the drug include dual relayed release (DDR) formulations (eg: dexlansoprazole MR).The DDR formulation consists of two different types of granules, each with a different pH-dependent dissolution profile. One type of granules releases the drug in the duodenum and yields a fast peak, whereas the rest of the drug is released in the distal part of the small intestine by the other type of granules. The latter is responsible for a later but more sustained peak prolonging the half-life to 6 h instead of 3 h for the conventional preparation.

Dexlansoprazole MR

Dexlansoprazole MR is a novel modified release formulation of dexlansoprazole, an enantiomer of lansoprazole [14]. This formulation results in a biphasic pharmacokinetic profile with prolonged drug exposure compared to lansoprazole. This drug combines an enantiomer of lansoprazole with a Dual Delayed Release (DDR) formulation designed to provide two separate releases of medication.Dexlansoprazole MR 60 and 90 mg/day leads to a higher percentage of intragastric pH > 4 compared to lansoprazole 30 mg. On the basis of these findings, two large identical Phase III trials were conducted including > 400 patients with erosive esophagitis [15]. Treatment with dexlansoprazole MR 60 or 90 mg/day during 8 weeks was compared with lansoprazole 30 mg/day. At week 8, healing rates were 92-95% of patients for dexlansoprazole MR compared to 86 – 92% for lansoprazole (not statistically significant). But the therapeutic gain (difference in healing rate) was small, that is, 5-7%. Similarly, post-hoc analysis revealed better healing of moderate-to-severe esophagitis (LA grade C or D), but even there the therapeutic gain was only 7%. When symptom improvement is considered, the median percentage of 24-h heartburn free days was comparable for the different treatments varying between 78 and 84%. The safety profile was also comparable. This study showed that dexlansoprazole MR is highly effective in healing erosive esophagitis and offers benefits over lansoprazole, particularly in moderate-to-severe disease. In a subsequent Phase III trial, patients with erosive esophagitis (n = 445) healed on dexlansoprazole MR were randomized to 6 months of treatment with dexlansoprazole (30 or 60 mg) or placebo [16]. The cumulative rate of maintaining mucosal healing (intention to treat) was 75 and 82% for dexlansoprazole MR (30 and 60 mg, respectively) compared to 27% for placebo. Although not statistically significant (low number of patients), the higher dose had better maintenance rates (85 versus 63%) in the patients with more severe esophagitis (LA grade C and D). Symptom control was also impressive with median percentage of 24-h heartburn symptom free days of 91 – 96%. Nocturnal symptoms were efficiently controlled; median percentage of nights without heartburn of 96 – 99. Both doses were well tolerated. Thus, Dexlansoprazole MR effectively maintained healing erosive esophagitis and symptom relief. The most commonly reported treatment-emergent adverse reactions (≥2%): diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, and flatulence. Dexlansoprazole MR was approved by the U.S. Food and Drug Administration (FDA) on January 30, 2009. Taken once-daily, this drug is approved for the healing of all grades of erosive esophagitis (EE) for up to eight weeks, maintaining healing of EE for up to six months, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

New proton pump inhibitors (PPIs)

Tenatoprazole

Tenatoprazole new PPI with an increased half-life. Chemically it is an imidazo-pyridine. The rate of activation of this compound to the active intermediates is slower than those of omeprazole, lansoprazole, and rabeprazole. Slow activation of tenatoprazole enables tenatoprazole binding to Cys822, which is located in the membrane domain, giving truly irreversible inhibition [17]. Tenatoprazole has a much slower metabolism than omeprazole, lansoprazole, and rabeprazole, giving a plasma half-life of about 6 h. The longer plasma half-life of tenatoprazole, combined with its ability to bind to Cys822, provides longer inhibition of gastric acid secretion. In healthy volunteers, tenatoprazole 40 mg provides a more profound acid suppression than 40 mg esomeprazole; the mean percentage of time pH > 4 on tenatoprazole and the mean pH during the night are significantly higher with tenatoprazole.[18,19]. Clinical trials evaluating its therapeutic effect in GERD patients or comparative clinical studies with esomeprazole have, however, not been published so far.

Alevium (AGN201904-Z)

AGN 201904-Z is an acid stable pro-drug of omeprazole. It is slowly absorbed throughout the small intestine and not just in the duodenum and rapidly converted to omeprazole in the systemic circulation. These properties translate in a prolonged residence time. Because one of the benzimidazolenitrogens is substituted, the compound is acid-stable, unlike any other PPI, and therefore does not require enteric coating. Furthermore, it is neutral pH-stable, thus not requiring alkaline solutions for stability in intravenous formulation, distribution, or administration. In a comparative study with esomeprazole, AGN 201904-Z produced a significantly greater and more prolonged (including nocturnal) acid suppression than esomeprazole. With once-daily Alevium (AGN201904-Z), the pH is stably maintained at greater than 4.0. Averaging pH values over 24 h or at night shows the remarkable advantage of Alevium, not only at night, but also during the day [20].

Potassium-Competitive Acid Blockers (P-CABs)

P-CABs are a new class of acid suppressive agents with a fast and prolonged effect. Drugs of this class block acid pumping by K+ competitive inhibition, so this class is called either acid pump antagonists or potassium-competitive acid blockers (P-CABs).The first core structure of a P-CAB developed in 1980 s was an imidazo-pyridine. A typical structure of this class having excellent inhibitory activity is SCH28080. Later, many P-CABs were developed. Gastric H+,K+-ATPase requires K+ in exchange for H+ to allow acid secretion in the canaliculus. Therefore drugs interacting with the binding of K+ ions to the proton pump will potently inhibit acid secretion. This principle has been the rationale to develop potassium-competitive acid blockers or P-CABs. P-CABs block gastric H+,K+-ATPase by reversible and K+-competitive ionic binding [21]. These agents are lipophilic weak bases with a high pKa and are stable at low pH. As a consequence, P-CABs are rapidly absorbed (peak serum concentrations between 0.5 and 1.5 h after oral administration) and will theoretically concentrate 100,000-fold in the canaliculus of the parietal cell compared to plasma levels. In this acidic environment, P-CABs are instantly protonated and subsequently bind ionically and reversibly to the proton pump. Potassium-competitive acid blockers most likely bind to a different binding site than K+, and act by docking the enzyme in a fixed conformation preventing the translocation of H+ ions into the canaliculus [22]. Because P-CABs inhibit the acid pump enzyme by K+ competition, P-CABs do not require acid-activation. Therefore, the inhibition by P-CABs is expected to be fast and effective. Rapid onset and efficacy to inhibit gastric acid secretion of P-CABs can also be attributed to their rapid absorption, their ability to concentrate extremely in the canaliculus, and their unique mechanism of action. Examples of P-CABs are AZD0865 (linaprazan), YH-1885 (revaprazan) and PF-03716556. So far, data on the clinical efficacy in GERD patients have only been reported for AZD0865. Two large randomized comparative trials have been

conducted in patients with erosive esophagitis [23] and non-erosive reflux disease [24]. In the first study, 1,521 patients with LA grades A – D and heartburn of moderate–to-severe intensity were randomized to AZD0865 25, 50 or 75 mg or esomeprazole 40 mg/day for 4 – 8 weeks. Despite the preclinical data indicating fast and almost complete acid inhibition by AZD0865, there were no significant differences in healing rates among AZD0865 doses or between AZD0865 and esomeprazole at 2, 4 or 8 weeks. Similarly, the onset of sustained absence of heartburn was comparable with that of esomeprazole. Second study was a randomized comparative clinical trial in which 1,469 NERD patients showed somewhat similar results. Patients with troublesome heartburn were randomized to receive AZD0865 or esomeprazole 20 mg/day for 4 weeks. Interestingly, although the percentage of time that intragastric pH > 4 was significantly greater for AZD0865 75 mg compared to esomeprazole (75 versus 60%), there were no significant differences among treatment groups in the cumulative incidence of sustained absence of heartburn. The median time to sustained absence of heartburn did also not differ between AZD0865 and esomeprazole. There was also a reversible raise in transaminases in 21 patients treated with AZD0865. The clinical development of this drug is terminated.

Studies conducted using a P-CAB, AZD0865, raise important questions as to whether improvement in acid suppression indeed translates into better clinical efficacy. One possible explanation for an increase in acid suppression (pH > 4) above the 50 -- 70% threshold not translating into additional clinical benefit is that gastric acid suppression is perhaps an imprecise surrogate for what is more directly contributory to the healing process: diminished esophageal acid exposure. In this regard, factors such as the rate of epithelial cell turnover and mucosal inflammation are important [25]. However, increasing the frequency of administration of AZD0865 to twice daily would be expected to outperform currently approved PPIs. Of particular relevance is the finding that about 20% of patients continue to experience symptoms even with twice-daily administration of any PPI. This finding is largely the result of de novo pump synthesis occurring after the drug has dropped below threshold in the blood, about 90 min after administration. A P-CAB with a long half-life would still be present and more effective than a PPI [26].

Recent advances in reflux inhibition strategy

Previously, treatments for GERD have focused on reducing heartburn, leading to the advent of various acid-suppressive and mucosal-protective agents. In contrast, regurgitation has received relatively little attention, based on the assumption that by rendering the refluxate nonacidic, patients would no longer be symptomatic. To a large extent, this belief has held true, because potent acid suppression, particularly by the powerful proton pump inhibitors, leads to resolution of symptoms in the vast majority of patients. However, it has become increasingly recognized that a small but significant subgroup of patients experience persistent reflux-type symptoms despite strong acid suppression, which may be result from weakly or nonacidic reflux. These patients are refractory to current standard therapies and incur a significant healthcare burden as a result of multiple medical consultations and unnecessary investigations. Given the success of the proton pump inhibitors in suppressing gastric acid output, it is generally believed that any further acid suppression would be both difficult to achieve and unlikely to offer additional therapeutic benefit. Clearly there is a demonstrated need for GERD therapies beyond the PPIs. Although these medications have provided a significant benefit, there remains an unmet clinical need for other medical therapies for patients with GERD -- in particular to those who may not achieve satisfactory results while taking PPIs. Thus there is a need for new for new therapeutic strategies reducing not only acid but also non-acidic reflux. More recently, research efforts have focused on alternative therapeutic targets, such as transient lower esophageal sphincter relaxations (TLESR).

Transient Lower Esophageal Sphincter Relaxations (TLESRs)

Together with the crural diaphragm, the lower esophageal sphincter (LES) is the most important contributor to the barrier that protects against gastro-esophageal reflux.[5]A defective LES pressure may be the major cause of reflux in a subgroup of patients and increasing the LES pressure might therefore be a potential target.

In 1980, it became clear that reflux mainly occurs during prolonged relaxations of the lower esophageal sphincter (LES) not related to swallowing [27]. These are now referred to as transient lower esophageal sphincter relaxations (TLESRs) [28]. Transient LES relaxations are prolonged LES relaxations which are not associated with swallowing that occur as a normal physiological response to gastric distention, allowing venting of gas from the stomach. Transient LES relaxations are mediated through a vago-vagal reflex pathway [29]. The major stimulus is distension of the proximal stomach, particularly the gastric cardia. The afferent signals are integrated in what is thought to be a pattern generator in the vagal nuclei. A stereotyped output from this generator leads to a complex response that includes relaxation of the lower esophageal sphincter (LES), inhibition of the crural diaphragm, and esophageal shortening [30]. TLESRs are found to be the main mechanism of both acid and non-acidic reflux in events both in healthy volunteers and patients, particularly in those with non-erosive reflux disease (NERD). Hence, pharmacological reduction of TLESRs could be a potential interesting target for treatment of GERD. Several drug targets have emerged from preclinical research of which a number of which have been tested in humans. The identification of pharmacologic receptors on the neural pathways mediating TLESR has opened the opportunity for the development of drugs that inhibit them and thereby gastroesophageal reflux. Several agents have been identified to reduce the triggering of TLESR, including CCK-A antagonists [31,32], anticholinergic agents [33,34], nitric oxide synthase inhibitors [35], serotonin type 3 ($5HT_3$) antagonists[36], morphine [37], somatostatin [38], N-methyl D-aspartate (NMDA) antagonists [39] and cannabinoid receptor agonist [40,41]. However, only γ-aminobutyric type B ($GABA_B$) agonists [42] and metabotropic glutamate receptor (mGluR) antagonists have shown any promise as therapeutic agents [43].

$GABA_B$ receptor agonists

$GABA_B$ agonists are probably the most promising emerging target for the treatment of GERD. GABA is an important inhibitory neurotransmitter in the CNS. It is abundantly present in the medullary centres controlling swallowing, esophageal motility and respiration. In particular, $GABA_B$ receptors are expressed in two important nuclei in the control of TLESRs, namely LES-projecting neurons of the motor nucleus of the vagal nerve, and the subnucleuscentralis of the nucleus tractus solitaries [43]. Activation of peripheral $GABA_B$ receptors inhibits gastric vagal mechanoreceptors and impairs vagal motor outflow, contributing to the inhibitory effect on the triggering of TLESRs.Baclofen, the prototypical $GABA_B$ agonist, was the first to be investigated for its potential therapeutic use in GERD. It was shown to reduce both TLESR and reflux episodes in healthy volunteers [44,45] and in patients with GERD [46,47]. In addition, baclofen increases the basal LES tone, an additional effect which might be beneficial in patients with a low tonic LES pressure. These studies reported that degree of inhibition of TLESRs in man varies between 40 and 60% as against 80% in dogs [48]. The lower degree of inhibition in man is most likely due to the fact that dosing is limited by the occurrence of side effects at higher dosages.

Arbaclofenplacarbil

Arbaclofenplacarbil (XP19986) is a prodrug for the pharmacologically active R-isomer of baclofen. This drug was designed potentially to treat GERD symptoms such as heartburn, spasticity and acute back symptoms with fewer side effects than baclofen. It has shown improved absorption, distribution, metabolism, and elimination properties compared with R-baclofen [49]. A multicenter, randomized, double-blind, crossover study comparing single doses of Arbaclofenplacarbil(AP) with placebo, was conducted to assess its

efficacy and safety for decreasing meal-induced reflux episodes in patients with gastroesophageal reflux disease (GERD). Different patients were enrolled at each of four escalating AP doses: 10, 20, 40, and 60 mg. Enrolled patients had GERD symptoms at least three times a week and 20 reflux episodes on impedance/pH monitoring over a period of 2 h. During study visits separated by periods of 3-7 days, patients received single doses of AP or placebo, followed by high-fat meals 2 and 6 h after treatment. The primary end point was the number of reflux episodes over 12 h after treatment. A total of 50 patients were treated; efficacy analysis included 44 patients who received both AP and placebo and had technically satisfactory impedance/pH data. For the combined data from all dose cohorts, there was a statistically significant (P=0.01) decrease in reflux episodes over 12 h after treatment with AP compared with placebo. The mean (s.d.) number of reflux episodes over 12 h after AP treatment was 50.5 (27.2), with a mean reduction of 10.4 (23.9) episodes (17%) compared with placebo, for which a mean (s.d.) number of 60.9 (35.3) episodes was observed. Heartburn events associated with reflux were reduced during treatment with AP compared with placebo. AP seemed to be the most efficacious in the 60-mg dose group, and was well tolerated at all dose levels. The study concluded that AP decreased reflux and associated symptoms with good tolerability in patients with GERD [50]. In a recently concluded randomized, double-blind, placebo-controlled study, the efficacy and safety of AP was evaluated over 4 weeks in subjects with symptomatic GERD. Though AP was well tolerated in this study it was observed that AP was not superior to placebo in reducing the number of weekly heartburn events over 4 weeks. It was also observed that response to PPI treatment before the study was associated with a response to AP treatment [51].

Lesogaberan

Lesogaberan (AZD3355) shares the same target as baclofen but with a more desired side effect profile. As opposed to baclofen, AZD3355 has been shown to reduce TLESR peripherally, which is an ideal mode of action to reduce side effects [52].The more desirable side-effect profile of lesogaberan is most likely attributed to $GABA_B$ transporters carrying very low levels of lesogaberan into the CNS [53]. In a randomized, double-blind, placebo-controlled, crossover study, the effects of lesogaberan was assessed on reflux and lower esophageal sphincter (LES) function when used as add-on treatment in patients with reflux symptoms despite proton pump inhibitor (PPI) treatment. In this study lesogaberan reduced the mean number of reflux events by approximately 35% compared with placebo. It also reduced number of TLESRs by 25% and increased LES pressure by 28% compared with placebo. The most common adverse events were headache (placebo: 11/27 patients; lesogaberan: 8/25 patients) and paresthesia (transient; placebo: 3/27 patients; lesogaberan: 5/25 patients) [54]. As a group, the $GABA_B$ agonists are the most extensively investigated and show the greatest promise as non-acid inhibiting anti-reflux agents. The biggest challenge for this group of drugs to be adopted into clinical use is to overcome side effects, particularly those that affect the CNS.

Scope of reflux inhibitors in GERD management

Reflux inhibitors are a new class of drugs reducing both acid and non-acid reflux by interacting with the main mechanism underlying reflux, that is, TLESRs. The possible uses of reflux inhibitor drugs will be strongly influenced by the magnitude of their antireflux effect. The more that a reflux inhibitor drug can approach the level of reflux inhibition of anti-reflux surgery, the more compelling will be the case for reflux inhibitor drugs to become a mainstream therapy in all types of reflux disease. Two classes of reflux inhibitors, that is, $GABA_B$ agonists and mGluR5 antagonists, are currently under development. The $GABA_B$ receptor agonists are the most promising new medications undergoing clinical trials because of their potential to decrease the frequency of TLESRs and their potentially low side-effect profile. These drugs may be effective as sole therapy but more probably will have most clinical use and value for additive therapy for PPI partial responders. The favourable

tolerability will probably make these agents more viable than baclofen, a drug that has severe limitation for use because of its excessive somnolence effect. The mGluR5 receptor antagonist ADX10059 is another promising drug undergoing clinical trials that has been show o decrease the number and duration of symptomatic reflux episodes. The recent removal of this drug from clinical trials leaves this an uncertain compound for further development in GERD therapy.

CONCLUSION

Despite the overall effectiveness of the current PPIs, many important clinical needs remain unmet, with more than 20%of patients with GERD experiencing recalcitrant symptoms, even when taking their drug twice daily. This finding is essentially a result of the short plasma residence time and lack of effect during the later part of the day and especially at night, which cannot be overcome by increasing the dose or frequency. To overcome these limitations, new inhibitors of the proton pump with a longer half-life, acting faster and longer, have been developed, including potassium-competitive acid blockers. Although proton pump inhibitors are highly successful entreating the vast majority of patients suffering from GERD, a small but significant proportion of patients have persistent symptoms caused by weakly or nonacidic reflux. The treatment focus in this group has shifted toward preventing reflux episodes from occurring, by inhibiting TLESR using reflux inhibitors. Through limited, small trials involving animals and humans, evidence is now accumulating to support the use of $GABA_B$ receptor agonists and mGluR antagonists. The main concern with all these agents is that of side effects, mainly CNS related. Despite the therapeutic efficacy of these newer agents, acid suppression with proton pump inhibitors remains the single most essential step in the management of GERD. The role of reflux inhibitors remains to be determined, but they most likely serve as an add on therapy option rather than replacement therapy to the proton pump inhibitors.

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