Tegoprazan as a New Remedy for Gastrointestinal Diseases in Comparison with Its Therapeutic Predecessors: A Mini-Review

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Abstract

Background: Potassium-competitive acid blockers (P-CABs), such as tegoprazan, are a new and diverse class of drugs that can completely block the potassium-binding site of gastric H^+/K^+ ATPase, potentially overcoming the limitations of proton-pump inhibitors (PPIs). A number of studies compared the effectiveness as well as the safety profile of tegoprazan to PPIs and other P-CABs for the treatment of gastrointestinal diseases.

Objective: The current review study evaluates the published literatures related to clinical pharmacology and clinical trials of tegoprazan for the treatment of diseases related to gastrointestinal tract.

Conclusion: According to the publications included in the study, tegoprazan was found to be safe and well-tolerated and can be used to treat a group of gastrointestinal diseases, including gastroesophageal reflux disease (GERD), non-erosive reflux disease (NERD), and H. pylori combination therapy.

Keywords: Tegoprazan, P-CABs, PPIs, gastrointestinal diseases, GERD, NERD, *H. pylori*.

1. INTRODUCTION

The groundwork for treating gastroesophageal reflux disease (GERD) and other acidity related gastric conditions was laid by the discoveries of H2 receptor blockers in the 1970s and proton-pump inhibitors (PPIs) in the 1980s [1-3]. However, PPIs have a drawback of being a prodrug as they need to become protonated before exerting their action on the gastric parietal cells [3-4]. Potassium-competitive acid blockers (P-CABs), unlike proton-pump inhibitors (PPIs), can antagonize the action of the hydrogen-potassium (H^+/K^+) ATPase protein [5-7]. P-CABs have the capacity to reach peak plasma levels promptly after oral administration and hence, can block H^+/K^+ ATPase without proton pump activation resulting in rapid acid inhibition in patients [3, 8].

Tegoprazan or (S)-4-((5,7-difluorochroman-4-yl)oxy)-N,N,2-trimethyl-1H-benzo[d]imidazole-6-carboxamide, one of the newest P-CABs, is a novel selective and reversible H^+/K^+ ATPase inhibitor (fig. 1) [9]. It is already approved in South Korea to treat gastric diseases like gastroesophageal reflux disease (GERD), erosive esophagitis (EE) and non-erosive reflux disease (NERD) [9-11]. The mechanism of action of tegoprazan is not different from that of other P-CABs like vonoprazan [11]. However, tegoprazan has some competitive advantages over other P-CABs, such as having a more rapid onset of action [9]. Some authors suggested that tegoprazan is more effective in suppressing nighttime gastric acid than other P-CABs and PPIs [12].

Several studies have compared the safety as well as the effectiveness of tegoprazan with PPIs in the treatment of gastrointestinal diseases as well [13]. Many of those studies showed that tegoprazan is not inferior to recently discovered PPIs such as lansoprazole [14]. In fact, like PPIs, this drug is indicated in the treatment of GERD, NERD, healing of gastric duodenal ulcers, treatment of upper gastrointestinal bleeding, and *H. pylori* eradication therapy. Through a thorough and systematic evaluation of the literature, this study is intended to analyze the updated knowledge of the safety and efficacy of tegoprazan in comparison to PPIs and other P-CABs to understand the potential of this relatively novel drug in the ever-growing market of gastrointestinal medications.

[Insert Fig. (1)]

2. METHODOLOGY

Literatures from PubMed and Google Scholar were searched to study the clinical pharmacology of tegoprazan from the year 2019 to 2022, as well as summarize all relevant clinical trials of those that are already licensed or

in development. The keywords used in the literature search were: 'CJ-12420, K-CAB, IN-A001, LXI-15028, RQ-00000004, GERD, NERD, PPI and Tegoprazan'. All review articles were excluded from the search.

3. HISTORY OF DEVELOPMENT OF P-CABs and TEGOPRAZAN

3.1. Drawbacks of PPIs and Alternative Approaches

The mechanism of action of PPIs is based on its ability to block the production of gastric acid by binding to H^+/K^+ ATPase as an antagonist [15-17]. Although PPIs are the most popular therapeutics in the treatment of gastric diseases, there are several drawbacks in their pharmacokinetic properties [18]. First off all, the maximum effect of PPIs does not appear until a certain period of continuous administration [19- 21]. In addition, due to their slow onset of action, PPIs do not adequately cure GERD reflux symptoms in two-thirds of patients after their first dose [22-23]. To be specific, PPIs require three to five days, on average, to reach their optimum level of stomach acid secretion inhibition [4, 24]. There are two reasons behind the slow onset of action of this group of drugs. Firstly, they need activation in the parietal cell and secondly, the target protein is not stable itself, moving from an active to an inactive state continuously [25–26]. Therefore, the dose adjustment is necessary depending on the number of active H^+, K^+ ATPase. Moreover, some external factors can influence the effects of PPIs, such as the cytochrome P450 (CYP) 2C19 polymorphism [27-28]. In addition, PPI's are generally less effective in stomach acid suppression at night [29]. All the facts mentioned above make them really disadvantageous, as more thorough and quicker symptom relief is required for GERD patients [30]. From the studies, it is evident that the first dose of PPI is not sufficient to control reflux symptoms in around two-thirds of symptomatic GERD patients, while over 50% of the patients still experience symptoms three days later [31–33]. Another study showed that a third of GERD patients said their symptoms were still present after completion of the PPI treatment and the medication did not work for them [34].

Extending the plasma residence time of PPIs had been one approach to improving PPIs treatment outcomes. For example, the residence time improvement through developing an omeprazole prodrug (AGN201904-Z) was a critical step. This drug at 600 mg in healthy volunteers showed a longer-lasting action than esomeprazole at 40 mg [35]. Later, less metabolically active drugs such as esomeprazole and dexlansoprazole were developed. That also helped in extending the blockade of H^+, K^+-ATPase. Further, a modified release dexlansoprazole formulation was developed to treat nocturnal acid breakthrough (NAB) [36–37]. The R-enantiomer of lansoprazole is dexlansoprazole, a PPI with a dual delayed-release formulation [38]. In a study, it was observed that within 2 hours and 5 hours following injection, the dual release system in the duodenum and small intestine reached 2 peak concentrations respectively [39]. In another study, scientists compared dexlansoprazole modified release (MR) 60 mg with lansoprazole 30 mg dosage and found similar efficacy [40]. However, after many years of in-depth study and advancements in PPI formulations, their limitations persist [41]. PPI restrictions are mostly connected to their similar modes of action. Thus, a more creative approach had been the development of other pharmacodynamic classes of drugs related to gastric acid suppression, such as potassium-competitive acid blockers (P-CABs) [21].

3.2. Development of Potassium-competitive Acid Blockers (P-CABs)

It was found in the early 1980s that gastric acid secretion is quickly, efficiently, and reversibly inhibited by P-CABs [42]. This fact drew attention of several pharmaceutical firms across the world [43]. Not all P-CABs were safe and effective. For example, an imidazopyridine named SCH28080 was one of the first P-CABs developed by Schering-Plough Corporation. It contains an imidazopyridine ring that has been linked to liver toxicity in human medical trials. In addition, it did not exhibit any more favorable benefits than traditional PPIs [44]. Still, this discovery sparked research on a number of P-CABs, including imidazopyridine derivatives, such as linaprazan, imidazonaphthyridine derivatives, such as soraprazan, imidazothienopyridines, such as SPI-447, quinolones, such as SK&F97574, pyrrolopyridazines, such as CS-526, pyrimidines, such as revaprazan and pyrrole derivatives, such as vonoprazan [45-50].

Revaprazan (YH-1885, Revanex) was the first P-CAB to be utilized in healthcare situations. Although it had a quick onset of action, it was found not better than the PPIs already on the market [51]. In case of linaprazan, another P-CAB, a dosage of 75 mg was found equivalent to 40mg esomeprazole for treating reflux esophagitis and managing heartburn [52]. However, like the previously developed imidazonaphthyridine named SCH28080,

linaprazan also caused liver damage and did not offer any more therapeutic advantages than 20 mg of esomeprazole for the treatment of GERD [53]. After the results of clinical study of linaprazan had been made public, additional researches for development of P-CAB's were paused for a long period of time [52-53].

Vonoprazan was the second P-CAB to be used in clinical settings. It quickly gained popularity due to its superior characteristics in onset of action, duration of action and potency [51]. The safety and effectiveness of a novel P-CAB, Tegoprazan (RQ-00000004/CJ-12420), 50 mg and 100 mg together with esomeprazole were compared in phase III studies for reflux esophagitis in South Korea (Table 1). The full and final findings of this investigation have not yet been published until 2018 [54]. In July 2018, Tegoprazan received approval in South Korea for the treatment of NERD and erosive esophagitis (EE) [54]. Following that, other agents such as DWP14012 and KFP-H008 have recently been developed [55-56].

Table 1. Summary of literatures containing clinical studies on safety tolerability of tegoprazan.

Author & Year	Study design & Duration	Phase	Dose	Comparator Drug	No. of patients included	Safety & Tolerability
Lee KJ, *et al* [54] Year: 2019	Prospective, study duration: 4-8 weeks	Multi-centre, randomized, double blind, parallel group comparison Study.	50 mg, 100 mg	Esomeprazole (40mg)	302 patients from korea with endoscopically confirmed erosive oesophagitis (EE)	Well tolerated.
Hwang JG, *et al* [57] Year: 2019	Prospective, study duration: 7–10 days	Randomized, single oral dose, two-treatment, two-period, two-sequence study.	100 mg	-	12 healthy patients (male)	Well tolerated, no major side effects were recorded.
Han S, *et al* [58] Year: 2019	Retrospective, study duration: 7 days	Randomized, phase I, double blind, placebo-controlled clinical trial.	50, 100, 200, 400 mg	Esomeprazole (40mg)	56 healthy male subjects without *H. pylori* infection	Well tolerated and it suppressed stomach acid quickly and effectively.
Cho YK, *et al* [14] Year: 2020	Prospective, study duration: 4-8 weeks	Randomized, phase 3, double blind, active control, multicenter study.	50 mg, 100 mg	Lansoprazole (30 mg)	306 gastric ulcer patients	There was no difference between the groups when it came to drug-related treatment-emergent adverse events.
Sunwoo J, *et al* [13] Year: 2020	Retrospective, study duration: 7 days	Randomized, open-label, active controlled study.	50 mg	Revaorazan (200 mg)	16 Helicobacter pylori-negative healthy korean male subjects	Well tolerated.
He J, *et al* [59] Year: 2021	Retrospective, study duration: 10 days	Randomized, single-center, double-blind, placebo-controlled study.	50, 100, 200 mg	Placebo	38 healthy Chinese subjects	No major adverse events were identified and well tolerated.
Yoon DY, *et al* [60] Year: 2021	Retrospective, study duration: 24 hours	Open-label, single-dose, three-treatment, three-period crossover study.	50 mg	-	12 healthy patients (male)	The Pharmacokinetics effectiveness as well as safety of tegoprazan 50 mg were not affected by the timing of meals.
Han S, *et al* [61] Year: 2021	Prospective, study duration: 7 days	Randomized, phase I, open-label, 2-period crossover study.	200 mg	PPI	24 healthy patients (male)	Independent of food effect.
Kim SH, *et al* [62] Year: 2021	Prospective, study duration: 4 weeks	Randomized, phase 3, double blind, placebo-controlled, multicenter study.	50 mg, 100 mg	Placebo	324 patients from Korea.	No adverse events.

4. TEGOPRAZZAN THERAPY IN GASTROINTESTINAL CONDITIONS

4.1. Tegoprazan therapy in gastroesophageal reflux disease (GERD)

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal illnesses seen in clinical practice, affecting approximately half of the all adults in the world [63]. GERD is essentially a dysfunction of the lower esophageal sphincter (LES), which can lead to heartburn and noncardiac chest discomfort [64]. Although PPIs are the most common treatment options for GERD and related symptoms, they have a number of drawbacks. Those include insufficient symptom relief, a slow onset of action, and a short duration of stomach acid suppression (fig. 2) [4, 65]. The discovery of P-CABs promised to overcome most of the pharmacological drawbacks of PPIs (fig. 2) [51].

Tegoprazan is a novel P-CAB with a rapid onset of action and the capacity to maintain long-term control over stomach pH (table 1) [58, 61]. According to Lee KJ *et al.,* a once-daily dose of tegoprazan 50 or 100 mg is comparable to esomeprazole 40 mg in the treatment of eosinophilic esophagitis (EE), a clinical condition similar to GERD [54]. In another study, Cho YK *et al.* found that tegoprazan 50 or 100 mg was not inferior to lansoprazole 30 mg once a day in the treatment of stomach ulcers [14]. According to the trial, the recovery rate was approximately 100% after 8 weeks [14].

Another study by Sunwoo J *et al.* showed that tegoprazan 50 mg suppressed stomach acid in GERD better than revaorazan 200 mg [13]. In a randomized clinical trial with GERD patients with no *H. pylori*, Han S *et al.* found that tegoprazan is well tolerated and exerts rapid and potent action in comparison to esomeprazole 40 mg [58]. Another study by the same research group concluded that tegoprazan's pharmacokinetic and pharmacodynamic qualities are unaffected by meals, therefore the medication can be given to patients regardless of their meal schedule [61]. Yoon DY *et al*. exerted in a study that tegoprazan 50 mg can be administered regardless of meal timing and hence further confirmed that fact [60]. According to another randomized control trial described by He J, *et al,* tegoprazan had dosage linearity after a single oral dose of 50 to 200 mg. In addition, it was found to reduce drug accumulation after 10 days of continuous treatment at the dose of 100 mg [59].

[Insert Fig. (2)]

4.2. Tegoprazan therapy in Non-erosive reflux disease (NERD)

NERD is characterized by persistent reflux-related symptoms in which there is no esophageal mucosal erosions or breaks on endoscopy [66, 67]. Previously, P-CABs were known to not provide a better beneficial result than of a normal dose of PPIs [53]. In the case of tegoprazan, however, Kim SH *et al.* compared tegoprazan (50 mg or 100 mg / day) with a placebo for 4 weeks and found that the patients receiving the treatment were fully relieved from heartburn and regurgitation [62].

4.3. Tegoprazan therapy in *H. pylori* infection

In 1983, it was found out that active chronic gastritis is associated with a spiral bacteria of the stomach mucosa named *Helicobacter pylori* [68]. According to global recommendations, first-line therapy for *H. pylori* infection should have a minimum eradication success rate of 90%. The typical PPI-based triple regimens usually fail to attain this eradication rate, owing to the increasing incidence of *H. pylori* strains resistant to clarithromycin and, metronidazole [69]. P-CABs such as tegoprazan based second-line *H. pylori* eradication outperforms PPI-based treatment by a large margin. Patients on a P-CAB based regimen showed a greater percentage of eradication (96 percent [264/274] vs. 91 percent [250/274], $p = 0.013$) than those on a PPI-based regimen [70]. In a clinical study conducted by Lee JW *et al.*, four antibiotics were combined with tegoprazan and the minimum inhibitory concentration (MIC) were determined [71]. Tegoprazan showed improved antibacterial efficacy against *H pylori*

as indicated by the MIC data. In addition, metronidazole susceptibility acquisition of tegoprazan (20.6%) was found more rapid than that of vonoprazan (4.7%) (fig. 3) [71].

[Insert Fig. (3)]

5. CONCLUSION

Tegoprazan is emerging as a new remedy for gastric acid-related disorders. It is well tolerated, and it suppresses stomach acid quickly and effectively in GERD (including EE), NERD, and *H. pylori* infections. It is an effective potassium-competitive acid blocker with a fast onset of action and it has the ability to keep gastric pH stable for a long time. Several studies compared tegoprazan with PPIs and P-CABs regarding efficacy, safety and tolerability. Tegoprazan was found effective and safe against the symptoms of GERD. In addition, unlike PPI's, the effectiveness of tegoprazan was found independent of food effect. However, in the case of NERD and *H. pylori* infection treatments, no specific comment can be exerted at this moment due to insufficient studies. Moreover, the comparative studies are still insufficient to understand the detailed competitive pharmacokinetic and pharmacodynamic advantages and disadvantages of tegoprazan in comparison to other PPIs and P-CABs. The authors hope that future studies will shed more light on this matter.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Figures

Figure (1). Chemical structure of tegoprazan

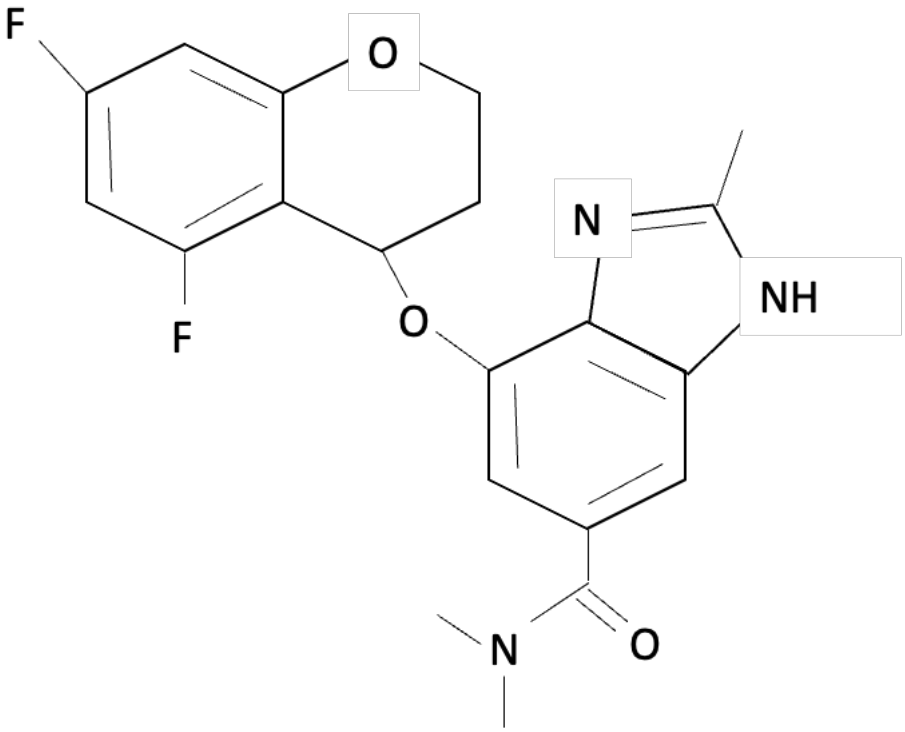

Figure (2). The comparison of tegoprazan with PPIs in the treatment of GERD.

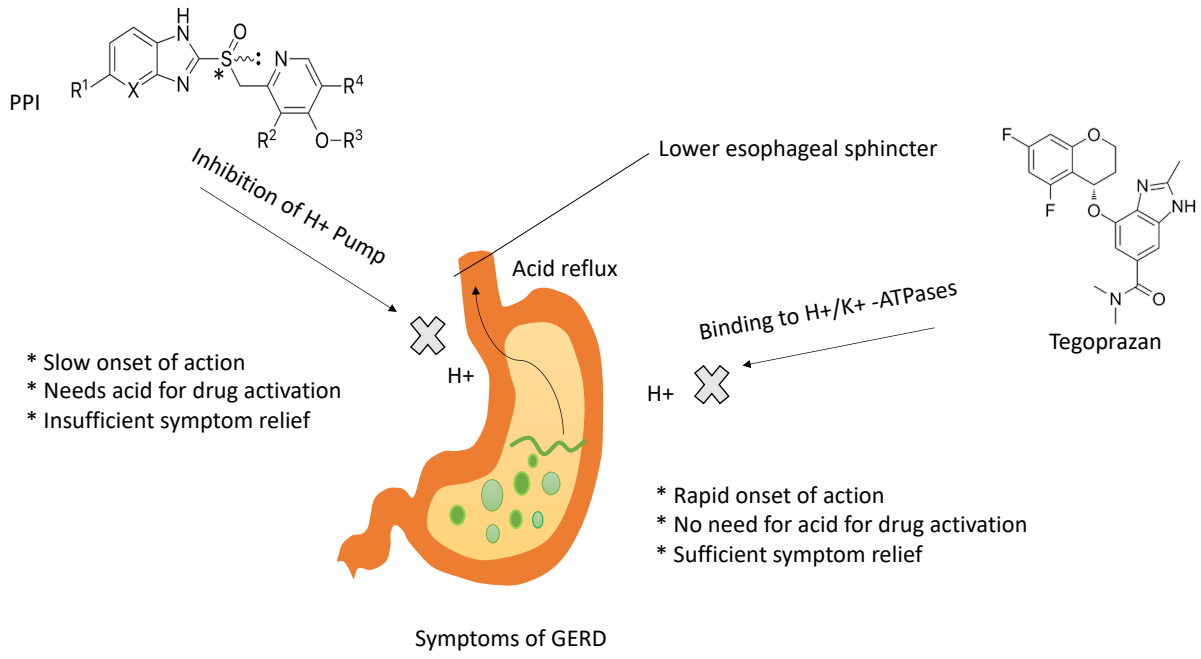

Fig. (3). Advantages of tegoprazan when used in combination therapy against H. pylori