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Beyond proton pump inhibitors: Vonoprazan in acid related diseases

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Keywords: Vonoprazan; Potassium-competitive acid blockers (P-CABs); Proton Pump Inhibitors (PPIs); Gastroesophageal Reflux Disease (GERD); Helicobacter pylori eradication; Acid-related disorders; Erosive esophagitis; Gastric acid suppression.

Abbreviations: PPI: Proton Pump Inhibitor; P-CAB: Potassium-Competitive Acid Blocker; GERD: Gastroesophageal Reflux Disease; H.pylori: Helicobacter pylori; VPN: Vonoprazan; NSAID: Nonsteroidal Anti-Inflammatory Drug; EE: Erosive Esophagitis; EoE: Eosinophilic Esophagitis; LDA: Low-Dose Aspirin; LA: Los Angeles; GU: Gastric Ulcer; DU: Duodenal Ulcer; FD: Functional Dyspepsia; MALT: Mucosa-Associated Lymphoid Tissue; ECL: Enterochromaffin Like Cells; Cmax: Maximum Plasma Concentration; RCT: Randomized Controlled Trial; LPZ: Lansoprazole; ESD: Endoscopic Submucosal Dissection; CYP: Cytochrome P450; ATPase: Adenosine Triphosphatase; TKI: Tyrosine Kinase Inhibitor; DDI: Drug–Drug Interaction

Abstract

Although Proton Pump Inhibitors (PPIs) are indispensable in the treatment of acid-related diseases, there are several restrictions in the use of PPIs. These include the prolonged onset of action, interindividual variability, and pH-dependence. Vonoprazan, a Potassium-Competitive Acid Blocker (P-CAB), has an extremely strong and long-lasting antisecretory effect. The following is an unstructured review that includes basic researches, Randomized Clinical Trials, and review papers, as well as real data and its use as an off-label drug. The drug has demonstrated enhanced rates of wound healing in patients with Gastro Esophageal Reflux Diseases and Peptic Ulcer Diseases, a higher eradication rate of Helicobacter pylori, and gastric acidity control compared with PPI therapy. In terms of the overall rebound acid secretion and hypergastrinemias, the safety profile of the drug is similar to that of PPI therapy. New indications of the drug involve GERD, Barrett's esophagus, and Zollinger-Ellison syndrome. This medication holds a promise of an entire paradigm shift in the management of various conditions associated with acid reflux. Their long-term basic research will assert its classified placement in this regard.

Introduction

The "gastric acid-related disorders" are actually a broad spectrum of diseases brought about by either excess or inappropriate secretion of the gastric juices. These include GERD, PUD, and Helicobacter pylori infections. The symptoms of heartburn, regurgitation, and even Esophageal injury are manifestations of GERD, which are brought about by the aberrant reflux of these juices into the esophagus itself [1]. As for gastric acid disorders, it would be important for effective management of such disorders considering the fact that such disorders actually threaten lives under extreme scenarios [1]. There are actually disorders brought about by the chronic aspect of disorders such that Esophagitis, Barrett Esophagus, and even

the increased susceptibility to Esophageal Carcinomas all exist. The catastrophic consequences of such disorders precipitating Bleeding, Perforation, and even gastric outlet obstruction actually exist under peptic ulcers [2]. Esophagitis and disabilities with regard to day-to-day activities are also precipitated by such disorders associated with gastro-esophageal reflux disease or GERD or even Esophagitis, which are actually quite common disorders such that refluxing precipitates actually through the reflux of stomach content into the Esophagus itself [3].

The "prevalence" of GERD under individuals belonging to the group under Northern America actually stands at an alarmingly high level of 18.1%-27.8%, European health groupings actually stands at quite high risk with regard to health actually at 8.8%-25.9%, The groupings under Asia stands actually quite low passing at 2.5%-7.8% [4].

Although GERD has historically been less common in Asian populations than in Western ones, it has recently exhibited a sharply rising tendency in Asia [5].

The impact of GERD on health care use and medical expenditure has been substantial because of the widespread nature and chronic characteristics of this disease [6]. GERD is the most common gastrointestinal illness that has been reported from outpatient clinic visits in the US [7], and the annual medical bills for this disease approximate $15 billion–20 billion [8].

Proton Pump Inhibitors (PPIs), for example, are widely used in the treatment of acid-related disorders including Gastro-esophageal Reflux Disease (GERD), stomach and duodenal ulcers, Ulcers induced by the use of NSAIDS, and the eradication treatment of Helicobacter pylori [9].

The traditional PPIs Include benzimidazole drugs, which irreversibly inhibit the enzyme hydrogen potassium (H+, K+)-ATPase, which is found in the parietal cells of the stomach and is primarily responsible for the production of H^+ ions, thereby making the PPIs more effective inhibitors of acid secretion in the stomach compared to the histamine H2 receptor antagonists [10]. Despite the widespread use of PPIs by prescribing them as the first line of treatment for the aforementioned diseases, it has become evident that there is a lot of difficulties which need to be improved [11]. First, it takes several days to reach the maximal effect. Due to the slow start of the effect, only one-third of the reflux symptoms of patients suffering from GERD can be relieved after the first administration of PPI medications. Further, one-half of them tolerate the pain even after taking the drugs for three consecutive days. Third, it has poor night-time performance. Finally, PPI can only function in an acid environment, meaning that the PPI is unstable under acidic conditions. Therefore, the enteric coating of the latter is required [12]. In addition, there is a considerable amount of empirical data available regarding the several negative consequences associated with the chronic administration of PPI, such as the induction of dementia, osteoporosis, ischemic-heart disease, and renal damage [13-15].

Vonoprazan (Voquezna®), the world's first PCAB-monoisoform, is also evaluated as part of combination regimens for H. pylori infections. In 2014, this drug received the first permit to launch within Japan due to its use [16]. Based on 'Phase 3 trial PHALCON HP: A randomized active-controlled clinical study in the USA and Europe, vonoprazan is now approved to use in combination with Amoxicillin or Amoxicillin in combination with Clarithromycin in the USA for adults to treat H. pylori infections [17], following vonoprazan's formulation change to address concerns over residues of nitrosamine impurities in earlier commercial product [18]. Moreover, vonoprazan is approved for use in adults for all grades of erosive esophagitis in the USA as monotherapy to relieve symptoms of heartburn to heal and maintain [19].

A new class of Potassium-Competitive Acid Blocker (P-CAB), named Vonoprazan (VPN), was developed as an alternative to traditional Proton Pump Inhibitors (PPIs) for the treatment of conditions associated with excess stomach acid [20]. While PPIs work by inhibiting the H^+/K^+ ATPase enzyme of parietal cells of the stomach, VPN fully and competitively inhibits the potassium-binding site of the aforementioned enzyme, leading to faster and sustained reduction of stomach acid secretion. This makes the drug highly ideal for people experiencing conditions associated with excess stomach acid, given its mechanism of action which makes it more reliable and efficacious than PPIs for acid suppression [21]. VPN works by reversibly blocking potassium ions to suppress the action of H^+, K^+-adenosine triphosphatase (ATPase), thus lowering stomach acid secretion [22]. The advantage of using VPN over PPIs resides largely in its insensitivity to acid-stimulated action and its capacity to reliably provide a reasonably fast and sustained anti-acid action irrespective of diet and genetic predispositions [23].

Pharmacology of potassium-competitive acid blockers

Mechanism of action

The distinct interaction of vonoprazan with the gastric pump is due to its unique chemical structure, which has been described as a pyrrole derivative with a sulfonyl group [24].

P-CABs have been found to be absorbed systemically, acting through reversible binding to the $H^+\backslash K^+$ ATPase pump on the parietal cell of the stomach, also known as the 'proton pump,' by inhibiting access of potassium ions to the potassium binding site of the proton pump, thereby decreasing the secretion of gastric juice [25]. PCABs bind to both the active and inactive form of the proton pump, which is located in the cytoplasmic as well as the extracytoplasmic regions, respectively. Their intracellular accumulation is also independent of pH. PCABs inhibit access of potassium ions to the potassium binding site of the pump through ion (reversible) binding [26].

In contrast to PPIs, which are acid-labile drugs, PCABs are stable in the acidic microenvironment of the stomach. Hence, they do not require a gastroprotector and chauffered nicely in neutral and acidic pH. The drug concentrate in the secretory canaliculi and are sequestered in the gastric mucosa. Directly and independently inhibit H^+/K^+-ATPase without activating them. Hence, they are not classified as a drug/prodrug [27].

Pharmacokinetics & pharmacodynamics

Chemically, Vonoprazan is represented as 1-[5-(2-fluorophenyl)-1-pyridin-3-ylsulfonylpyrrol-3-yl]-N-methylmethanamine [33]. Vonoprazan fumarate has a novel chemical structure that belongs to the pyrrole derivatives, with a different chemical structure from the past P-CABs, such as

SCH 28080 and AZD0865, with a benzimidazole ring, or revaprazan, with a pyrimidine ring [34]. Vonoprazan's basic pKa value of 9.06 enables the compound to remain unchanged in the bloodstream, hence diffusing easily into parietal cells. Later, when inside the highly acidic secretory canaliculi, the compound becomes protonated, hence "trapped," leading to a marked concentration. The process of acid trapping has been shown to significantly increase the affinity of the compound with H^+/K^+-ATPase, an activity that leads to rapid, potent, and sustained inhibition of gastric acid secretion. Indeed, this is a marked difference from the past P-CAB agents [35]. In animal or simulation studies, Vonoprazan showed a marked affinity to the stomach parietal cell during the resting state or during the actively secreting state. Moreover, the affinity during the resting state was shown to be higher than the actively secreting state, but lansoprazole showed high affinity within the actively secreting state. Vonoprazan's basic pKa (9.06) enables the compound to easily diffuse into the cell without needing a protonated form, hence leading to [36].

Pharmacokinetics

It is quickly absorbed, with maximum concentration achieved in 2 hours, although the half-life (t1/2) in human plasma is much longer (approximately 7 hours in Japanese subjects dosed with 20 mg vonoprazan in an overnight fasted state) than in PP is (which have half-lives of t1/2=1 to 2 hours), as depicted in pharmacokinetic profile. Moreover, vonoprazan does not necessitate acid-catalysis for activation. Consequently, in investigation of acid suppression activity, vonoprazan was shown to have equal efficacy when taken either pre- or post-breakfast administration [37]. Notably, vonoprazan exhibited potent activity in acid suppression which persisted for an extended period from the very first day of administration in a dose-dependent manner, cumulating over an ensuing seven days. A practically complete achlorhydria was induced in Japanese as well as UK subjects treated with vonoprazan (40 mg) [38]. It is important to note that vonoprazan-induced acid inhibition was considerably quicker and more profound compared to PPIs. The effects became observable already from the very first day of administration. Even on Day 7, namely during already seven days when PPIs stabilize to reach an equal acid suppression effect, vonoprazan in comparison to esomeprazole (20 mg) and Rabeprazole (10 mg) clearly outperformed these two medications during acid-reducing activity (i.e., percentage of cumulative time within which intragastric pH >4 was maintained in 24 hours) [39].

Drug-drug interactions

The study evaluated possible Drug Drug Interactions in vitro with rat liver microsomes and in vivo with ultra-performance liquid chromatography-tandem mass spectrometry for the detection of probe drug metabolites in rat plasma.

Vonoprazan inhibits CYP3A4 (IC50: 22.48 μM), CYP2C9 (IC50: 18.34 μM), CYP2D6 (IC50: 3.62 μM), and CYP2B6 (IC50: 3.68μM Different cytochrome P-450 isoenzymes catalyze the two processes of initiation through hepatic metabolism, which constitute the biotransformation of clopidogrel. However, CYP2C19 is the major one involved in the process of activation. The hepatocellular metabolism of vonoprazan also takes place largely through CYP3A4. The combined therapy of vonoprazan or esomeprazole and clopidogrel must, therefore, be considered jointly due to the following reasons. Esomeprazole, on the other hand, is metabolized through the liver, largely CYP2C19, with a minor contribution from CYP3A4. However, they both can potentially inhibit CYP2C19, the major site of the possible metabolism and activation of clopidogrel in the liver [41].

The co-administration of voriconazole notably raises blood levels of vonoprazan due to the inhibitory effect of voriconazole on CYP3A4 metabolism. This leads to a high drug concentration and a decrease in its clearance. Excess drug can produce intense inhibition of gastric secretion and also increase the risk of hypergastrinemia due to a higher drug concentration [42].

Vonoprazan showed a strong inhibitory effect on venlafaxine metabolism, which resulted in a significantly increased systemic exposure of venlafaxine and its O-desmethyl venlafaxine metabolite [43].

Vonoprazan shows higher strength and longer duration of gastric acid suppression. The co-administration of vonoprazan with Tyrosine Kinase Inhibitors leads to substantial underexposure, possibly because of the pronounced bioavailability reduction at higher gastric pH levels. Vonoprazan is contraindicated or to be used cautiously with these TKIs, possibly mandating alternative approaches to acid suppression [44].

Vonoprazan clinical applications and efficacy

GERD and erosive esophagitis

The most relevant Randomized Controlled Trials which studied and demonstrated effectiveness of conventional Proton Pump Inhibitors and Potassium-Competitive Acid Blocker (Vonoprazan) in managing GERD and Esophagitis is summarized below. The main clinical findings, relief in early symptoms, rate of healing, and trial parameters presented in the tables highlight key determinants.

Faster healing of early lesions and similar heartburn relief for vonoprazan, greater efficacy for severe erosive esophagitis.

It provides faster relief of symptoms for severe erosive esophagitis, maintains long-term healing with reduced recurrence rates within 24-48 weeks, and has healing rates that are comparable to or even greater than standard PPIs [48].

The reduction of the average total GERD-Q score (from 11.96 to 8.92, $p<0.001$) indicates that vonoprazan significantly decreased the incidence of symptoms related to reflux. Moreover, patients with vonoprazan showed significantly lower scores compared to patients with PPI therapy for the incidence of heartburn, regurgitation, and lack of sleep associated with GERD, respectively.

The effectiveness of vonoprazan 20 mg was significantly greater than Rabeprazole 10 mg and 15 mg of Lansoprazole added with Esomeprazole 10 mg and Omeprazole 10 mg. This implies that the dose can also be increased to 20 mg because vonoprazan 10 mg was not effective to prove its potential to produce a superior effect of GERD maintenance over the recommended PPIs in Japan [50].

H. Pylori eradication

Heliobacter pylori are the type of microaerophilic, spiral-shaped, gram-negative bacteria that can be found inhabiting the human stomach mucosa, along with being the prime cause of many cases of gastro duodenal diseases [51].

H. pylori often causes chronic gastritis, which can also be associated with severe symptoms such as stomach cancer and MALT [52].

PPI-triple therapy has remained the mainstay of H. pylori therapy for over two decades in various parts of the globe including the United States of America. This typically includes PPI, Clarithromycin, and either Amoxicillin or Metronidazole [53]. The efficacy rate has, however, decreased to lower than 80% in Europe and United States [54] owing to high levels of resistance to Clarithromycin [55].

Japan sees high prescribing of VAC triple therapy as the main treatment for anti-H. pylori, which has over a million prescriptions per year [56], although resistance levels of clarithromycin to H. pylori are high [57].

Both Regimens had high rates of eradication; this includes 92.5% for high dose Amoxicillin/Vonoprazan, as well as 88.9% for the low dose. Strict adherence exceeded 955 in all groups, although adverse reactions were of mild nature (12-15%) without any severe events. This draws the final conclusion that Vonoprazan's strong acid suppression ability helps in amoxicillin therapy [58].

Dual therapy of vonoprazan and amoxicillin Eradication rates: 92.9%, noninferior to 91.9% for triple therapy, and similar safety profiles. The dual therapy regimens were superior when infections were caused by organisms resistant to clarithromycin, 92.3% vs 76.2%. A 7-day home treatment of vonoprazan + amoxicillin is thus effective for eradication without having to resort to clarithromycin, especially when resistance rates are high [59].

Ulcers caused by NSAIDs

Owing to the fact that non-steroidal anti-inflammatory drugs and Low Dose Aspirin are recognized for their immunosuppressive action on the mucosa that resists the acidity of the stomach through pathways related to the suppression of natural prostaglandins in the stomach mucosa [60], they are associated with unfavourable outcomes of bleeding ulcers and ulcers of the stomach or intestine [61]. As many as 20% of Asians are recognized to fall ill with Peptic ulcer diseases, which include acid-related chronic conditions [62]. Among patients getting treatment for bleeding ulcers, 7.6% had been using LDA in Japanese research [62].

In a separate study, it was determined that incidence of ulcers among of Low dose Aspirin-users was between 11.9% -15.2%, regardless of formulation of Aspirin [63].

In addition, certain observational studies have pointed out the increased use of LDA [64] as a major contributing factor for the onset of bleeding ulcers. 38(12.4%) of 305 patients on LDA had endoscopically detected ulcer lesions, as reported in the Japanese single institutional study [65].

Untreated ulcers can become recurrent or present as acute gastrointestinal bleeding. These are usually found in the stomach (gastric ulcer, GU) or in the duodenum (duodenal ulcer, or DU) [66].

Helicobacter pylori infection and Nonsteroidal Anti-Inflammatory Drug (NSAID) use are the two major risk factors associated with gastrointestinal injury and acid-related peptic ulcers [67].

When undergoing Low dose Aspirin therapy, proton pump inhibitors are used for the prevention of recurrent stomach or duodenal (peptic) ulcers; however, recurrent ulcers have been observed in some individuals showing that secondary prophylaxis is not completely effective [68].

Safety and tolerability

The three endpoints tested in all six trials included the healing rates at the 2-week, 4-week, and 8-week endpoints. Generally, the trial established that the healing rates in erosive esophagitis margins were superior in Vonoprazan compared to PPI at the 2-week, 4-week, and also the 8-week endpoint [72].

A total of 40,937 patients with a history of lansoprazole use had 500 reported cases of microscopic colitis. On the other hand, among 11,102 patients with a history of vonoprazan use, there were only 55 reported cases of microscopic colitis [73].

Results from some research inquiry that excessive use of acid-reducing medication can alter the microbial ecosystem of the intestines, thus predisposing one to an increased risk of Clostridium difficile Infection [74].

For patients treated with vonoprazan and esomeprazole, H. pylori test negativity was observed in 20 out of 20 (100%) and 17 out of 18(94.4%) cases [75].

The listed adverse reactions of the drugs vonoprazan dual pak(both the vonoprazan and the amoxicillin) and vonoprazan triple pak (vonoprazan,amoxicillin, and clarithromycin) that occurred in ≥2% of patients include Nasopharyngitis, Diarrhea, Constipation, Flatulence, Dyspepsia, Headache, and Abdominal pain.The serious adverse reactions listed, though <2% of patients, include but are certainly not limited to,blood disorders such as anemia and neutropenia, bone fractures, infections, and cardiac abnormalities such as QT prolongation [16].

Compared to PPIs, vonoprazan, which is safer and more tolerable, could decrease cases of diarrhea and loose stool in patients with acid reflux [76].

Patients with clarithromycin-resistant strains treated with the VAC regimen had significantly higher eradication rates than those treated with the lansoprazole, amoxicillin, and clarithromycin regimen in post hoc analysis performed in phase III research [77].

Vonoprazan had no impact on kidney function, according to the clinic data analysis of a small-scale randomized research trial involving patients with diabetic nephropathy, since serum creatinine levels and Estimated Glomerular Filtration Rate remained unaltered after therapy. Relative to pretrial levels, a small, significant reduction was noticed in proteinuria, whereas there was little difference in PPI control. The tolerability was adequate, with no cases reported for acute kidney injury or kidney-associated adverse reactions [78].

Studies conducted on rats and rabbits at therapeutic doses of the drug showed insignificant abnormalities, although severe exposure caused mild skeletal retardations and decreased fetal weights, usually with maternal toxicity. In general, the outcome of the tests indicates the teratogenic potential is very low at the standard doses, but with a note of concern due to the unavailability of any human pregnancy data [79].

Emerging indications and off-label uses

Vonoprazan and PPIs are among the most used acid inhibitors for the management of bleeding and ulcers due to ESD. As stated in some research, vonoprazan proved as effective as PPIs for ulcers resulting from ESD [80].

Nonetheless, some studies showed a superiority of vonoprazan over PPIs in repairing ulcers resulting from ESD [81,82].

As stated by Takahashi et al., shrinkage ratios of less than 90% at the fourth week are indicative of delayed ulcer healing [83].

Within this small population of EoE patients, the study conducted by Kuzumoto et al. revealed that the response rates for symptoms, endoscopy, and histology for vonoprazan 20mg were comparable to PPIs, and while numerically it was among the higher rates of complete relief of symptoms (75.7%), it was not statistically different [84].

Response rates in the 10mg and 20mg vonoprazan arms at the second week were 31.0% and 35.7% (p=0.937), at week four in the study they were 75.8% and 78.6% (p=1.00), and 72.4% and 75.9% at week 8 (p=0.24). There was no significant difference between the response rates in the two groups [85].

Very little information is available regarding the dosage of vonoprazan in treating Functional Dyspepsia [86].

Currently, four meta-analyses of Vonoprazan revealed conflicting results. One trial revealed Vonoprazan to be superior to PPIs in ulcer healing at 8 weeks after ESD [87], and in another trial, Vonoprazan was found to accelerate the healing process at 4 and 8 weeks after ESD [88].

A total of 13 studies, including 1,510 subjects, were identified which included reports of healing of ulcers and/or ratios of shrinkage of ESD-induced ulcers after vonoprazan [89].

Real world data

The reported adverse events were abdominal pain, palpitations, headaches, loose motion, and nausea & vomiting. Among these, abdominal pain recorded the least number, while loose motion recorded the highest. Zuberi et al. observed that vonoprazan dual therapy had fewer instances of adverse events and proved more tolerable than conventional triple therapy. Only a few patients in the vonoprazan group showed moderate events of nausea, vomiting, bloating, & diarrhea, yet none of these events were severe enough to warrant discontinuation of this therapeutic regimen [90].

A comparison of the safety and effectiveness of triple therapy with vonoprazan and triple therapy with PPI was carried out. The incidence of side effects was much lower and the tolerance was higher in the vonoprazan-based triple therapy compared to PPI-based therapy, as stated in the meta-analysis [91].

Likewise, another retrospective study found the efficacy of vonoprazan in PPI-resistant patients with GERD. In this study, vonoprazan 10 mgdaily was given to 24 patients with PPI-resistant GERD. After one month of vonoprazan administration, there was a significant reduction in Izumo scoring (5.8±1.7 to 1.9±1.9, p<0.001), and symptoms of GERD also improved in 88% (21 out of 24) and 42% (10 out of 24) of patients without any adverse effects. In conclusion, vonoprazan 10 mgdaily is effective in PPI-resistant patients with GERD.

Out of 1,642 patients, 840(51.2%) were male and 802(48.8%) were female with a mean age of 39.81±14.61 years. The mean score of GerdQ was 20.37±15.87 at baseline, 7.24±8.15 in the second week, and 3.70±6.31 in the fourth week of treatment respectively (p<0.001). The eradication rate of H. pylori was 90.74%. The great percentage of patients had regurgitation of acid or heartburn for less than one day a week in more than 70% of the weeks. The great percentage of patients, 78.13% (1,283 patients), had a good compliance rate. The total patients with a mild side effect were 37(2.3%) patients.

Vonoprazan showed a marked efficacy in the prophylaxis of GERD symptoms, reducing the risk of the disease by alleviating symptoms, and it also completely eradicated the H. pylori infection with a high efficacy. In general, the drug Vonoprazan has shown effectiveness in treating PPI-resistant reflux esophagitis patients.

The trial involved 24 patients with PPI-refractory reflux esophagitis, 58.3% of whom had severe erosive esophagitis. The endoscopic healing of patients with esophagitis was 87.5%, including patients with severe esophagitis at 85.7%, at 4 weeks after switching from PPI to vonoprazan at a dose of 20 mg per day. Also, the symptoms of GERD were markedly improved the next day after changing anti-reflux drugs [93].

Vonoprazan markedly decreased the incidence of disorders caused by the release of stomach acid because it has a strong inhibitory effect on the release of the acid [94]. More than 95% of the subjects received either PPI or PCAB to prevent mucosal damage caused by aspirin [95].

The cumulative body of comparative data indicates that P-CABs like vonoprazan and tegoprazan are genuine, or even preferable, alternatives to PPIs in the case of acid-related diseases (GERD, esophagitis, ulcers) where rapid, potent, or sustained acid inhibition is needed [96,97].

Future directions and research gaps

Most of the research on Vonoprozan has continued to focus on the eradication of H. pylori. Vonoprazan dual and triple therapies are more effective than PPI-based regimens, especially in high clarithromycin-resistant rates, according to the latest research on RCTs and meta-analyses available [101]. There is a significant information gap with regard to pediatric/teenager GERD, with current pharmacokinetic studies in children aiming at identifying appropriate dosing, and expanding indications within the young group [99]. Long-term safety studies, such as VISION, are also important for tracking potential hazards like mucosal hyperplasia, Enterochromaffin Like Cells changes or neoplasia because of the potent and sustained acid-suppressive effect that vonoprazan has, compared with PPIs [102]. Big clinical trials in China and Asia are evaluating effectiveness in various combinations of H. pylori resistances, real world compliance rates, and differing healthcare environments; worldwide acceptance needs experiences from diverse populations [102] Vonoprazan proved to be more effective in healing and maintaining compared to Lansoprazole in both mild and severe Erosive Esophagitis despite being costly. The annual expenses for the Vonoprazan 10&20 mg group were expected to be €833.28 & €166.56 respectively, whereas for the Lansoprazole, the cost was estimated to be €330.96. Vonoprazan proved to be more effective in healing irrespective of the difference in the cost. Healing percentages compared to 71.1% of the healing rates of the Lansoprazole group for the Vonoprazan 10&20 mg in the case of mild disease were found to be 81.3% & 82.3% respectively. In the case of severe disease, healing percentages compared to the healing rates of the 61.5% & 74.7% of the Lansoprazole group for the Vonoprazan 10 & 20 mg were found to be 77.2%. Vonoprazan is costly, clinically effective in case The long-term use of vonoprazan has not been demonstrated to exert any kind of significant safety risk in randomized trials and programs, such as the VISION program, despite the fact that the highly effective acid inhibition and resulting elevation in gastrin concentrations mandate constant safety surveillance. The cost-effectiveness evaluations in progress are showing varying region-dependent

results, which are nonetheless positive. Worldwide large-scale safety registration programs and real-world comparisons as well as new economic models are required for the precise determination of the long-term vonoprazan safety benefits and cost value in healthcare settings [1,102,104].

Conclusion

Vonoprazan, as the first P-CAB on the market, substantially surpasses PPIs in terms of pharmacological efficacy and clinical efficacy. Its rapid onset, phi independent activation, and CYP2C19 independent degradation allow frequent and prolonged acid reduction, resulting in better healing of erosive esophagitis, increased rates of H. pylori eradication, and successful treatment of refractive conditions. Safety, tolerance in short/intermediate term therapy are established based on results of major RCTS, while hypergastrinemia in long term therapy, CYP3A4 mediated pharmacokinetic interactions, therapy in patients with hepatic impairment, pediatrics, or cost issues remain as yet unclear. Conclusion: Vonoprazan is a viable option and often a superior alternative to PPIs, offering a lot of promise regarding shifting practice patterns for a spectrum of acidic diseases. If safety in the long term and cost performance continue to provide a suitable return on early efficacy, it should have a more defined role within that spectrum.

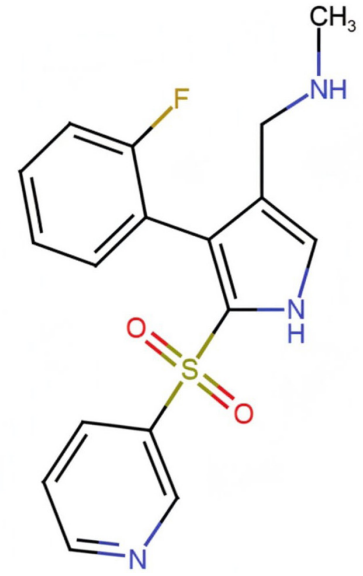

Figure 1: Chemical structure of vonoprazan.

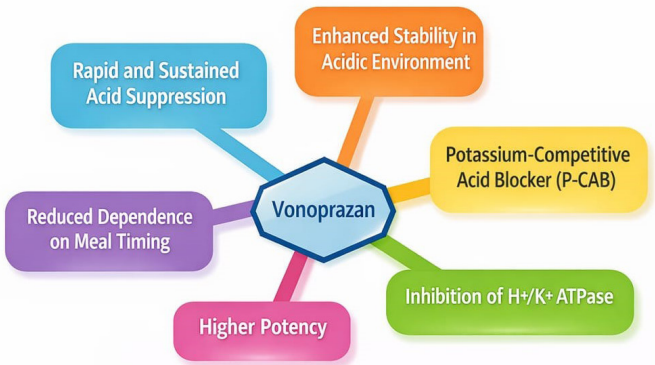

Figure 2: Key pharmacological features of vonoprazan as a Potassium-Competitive Acid Blocker (P-CAB).

Figure 3: Overview of current and emerging clinical uses of vonoprazan in acid-related gastrointestinal disorders.

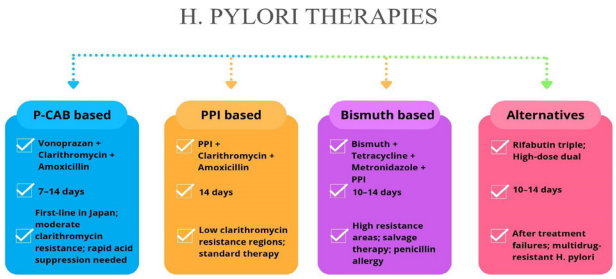

Figure 4: Overview of recommended *Helicobacter pylori* eradication regimens, including Potassium-Competitive Acid Blocker (P-CAB), Proton Pump Inhibitor (PPI), bismuth-based, and alternative therapies.

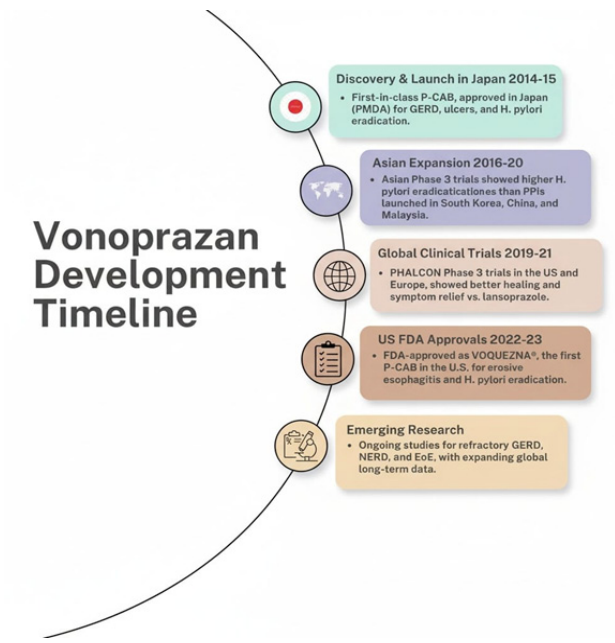

Figure 5: Key milestones in the clinical development and global approval of vonoprazan.

Table 1: Comparison of P-CABs and PPIs.

Parameter	Potassium-Competitive Acid Blockers (P-CABs)	Proton Pump Inhibitors (PPIs)
Chemical stability in acid	Stable under acidic conditions	Unstable in acid; require enteric coating for protection
Prodrug nature	Active in native form	Administered as prodrugs; activated in acidic environment to form sulfenamide intermediates
Binding characteristics [28]	Reversibly and ionically block K^+ access to the gastric proton pump	Form irreversible covalent bonds with cysteine residues on active H^+/K^+-ATPase pumps
Elimination half-life (hours) [29]	Approximately 6-9 hours	Typically 1-2 hours
Timing of administration	Can be taken without regard to meals owing to longer duration of action [30]	Should be administered 30-60 minutes before food intake for optimal activation during peak acid secretion [31]
Dosing frequency for maximal acid suppression (days) [32]	Once daily often sufficient	Usually requires 3-5 days for maximum effect
Representative drugs	Vonoprazan, tegoprazan, fexuprazan, linaprazan, revaprazan, keverprazan.	Omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole

Table 2: Randomised clinical trials comparing vonoprazan and lansoprazole for the treatment of erosive oesophagitis.

Study (Year)	Design/Patients	Treatment	Comparator	Healing rate (Eight weeks)	Early effect (two- four weeks)	Symptom relief/Key findings
Randomised Clinical Trial: Vonoprazan vs Lansoprazole for Healing of Erosive Oesophagitis. Alimentary Pharmacology & Therapeutics [45].	Multicentre randomized controlled trial conducted in Japan involving patients with erosive esophagitis (LA Grades A-D).	Vonoprazan 20 mg once daily	Lansoprazole 30 mg once daily	99.0% vs 95.5%	Not reported	Both groups showed high healing rates; Vonoprazan demonstrated sustained healing during maintenance.
Randomized, Double-Blind Study Comparing Vonoprazan and Lansoprazole in Asian patients with Erosive Esophagitis Gut [46].	Phase III double-blind multicenter trial in Asian patients with erosive esophagitis.	Vonoprazan 20 mg once daily	Lansoprazole 30 mg once daily	92.4% VS 1.3%	75% vs 68% after two weeks (Vonoprazan considerably higher)	Vonoprazan produced faster restoration in patients with more severe Esophagitis (gradesC/D).
A Randomized trial comparing Vonoprazan and Lansoprazole for the treatment and maintenance of Erosive Esophagitis. Gastroenterology [47].	Large international randomized controlled trial including North American and European patients with mild to severe erosive esophagitis (Grades A-D).	Vonoprazan 20 mg once daily	Lansoprazole 30 mg once daily	92.9% vs 84.6%	Faster healing at 2 weeks, especially in severe (Grades C/D cases)	Vonoprazan provided faster early healing and comparable heartburn alliievation; better efficacy in severe erosive esophagitis.

Table 3: Randomised controlled trials evaluating vonoprazan for ulcer healing and secondary prevention of NSAID- and low-dose aspirin–associated peptic ulcers.

Study	Design / Sample size	Primary endpoint	Key results
Mizokami et al. Gut 2018 (NSAID secondary prevention) [69]	RCT, n=642 (VPZ 10 mg, VPZ 20 mg, LPZ 15 mg)	Recurrent peptic ulcer at 24 weeks	VPZ10: 3.3%, VPZ20: 3.4%, LPZ: 5.5%; Non-inferior
Kawai et al. Gut 2018 (LDA secondary prevention) [70]	RCT, n=621 (LPZ 15 mg, VPZ 10 mg, VPZ 20 mg)	Recurrent peptic ulcer at 24 weeks	LPZ: 2.8%, VPZ10: 0.5%, VPZ20: 1.5%; Non-inferior
Miwa et al. AP&T 2017 (Gastric ulcer) [71]	RCT, GU: VPZ n=231, LPZ n=225	Healing of gastric ulcer at 8 weeks	VPZ: 93.5%, LPZ: 93.8%; Diff -0.3% (95% CI -4.75 to 4.21); Non-inferior
Miwa et al. AP&T 2017 (Duodenal ulcer) [71]	RCT, DU: VPZ n=178, LPZ n=180	Healing of duodenal ulcer at 6 weeks	VPZ: 95.5%, LPZ: 98.3%; Diff -2.8% (95% CI -6.40 to 0.75); Non-inferiority not confirmed

Table 4: Ongoing and recently registered clinical trials evaluating vonoprazan in *Helicobacter pylori* infection and gastro-oesophageal reflux disease.

Trial/Study	Focus/Patient population	Status/Key notes
VA Dual Sequential Therapy NCT06929962 [98]	Vonoprazan + amoxicillin dual therapy for treatment-naïve Helicobacter pylori infection	Started April 2025; estimated completion December 2026. Open-label, randomized, multicenter.
Phase 1 pediatric GERD trial (adolescents or children with GERD) NCT05343364 [99]	Pharmacokinetics, pharmacodynamics, and safety of vonoprazan (10 or 20 mg daily) in pediatric patients with symptomatic GERD	Listed as concluded or updating (latest registry update April 2025) for adolescents; similar design for children 6-12 years.
NCT06564246-Vonoprazan vs Pantoprazole in GERD [100]	Vonoprazan 20mg vs Pantaprazole 40 mg in GERD patients; a comparison	Began in 2024, with a primary completion date of 2026, recruiting at the moment

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