Vonoprazan vs proton pump inhibitors: A comparative review of efficacy, safety and cost effectiveness in pepetic ulcer, GERD, H. Pylori infection

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Abstract:- Proton pump inhibitor medication is the standard treatment for gastro-oesophageal reflux disease (GERD), one of the most common illnesses in the world. Nonetheless, about 40% of patients have complained of resistance to this treatment in one way or another. Recently, vonoprazan received approval to treat GERD. Because VPZ was not impacted by pH variations in preclinical research, it was 1.2–2 times more effective than PPI in both in vitro and in vivo settings. It was demonstrated that VPZ was far more economical than PPI. According to the article's findings, VPZ is more effective, safe, and economical than PPI for treating reflux diseases and eliminating H. pylori.

Vonoprazan should therefore be used instead of traditional PPIs for these conditions.

Vonoprazan and other potassium-competitive acid blockers (P-CABs) are a new and diverse class of medications that competitively block the potassium binding site of gastric H+/K+ ATPase, potentially getting around the drawbacks of proton-pump inhibitors. The effectiveness of vonoprazan against proton-pump inhibitors (PPIs) for treating acid-related diseases was assessed in many research; as a result, P-CABs exhibit the same indications as PPIs:

Key words:- PPI, H2-receptor antagonists vonoprazan, gastric ulcer, P-CAB, peptic illness, potassium-competitive acid blockers, peptic ulcer, haemorrhage, Adverse effects

1. INTRODUCTION

The occurrence of gastroesophageal reflux diseases and H. pylori-induced duodenal and gastric ulcers is widespread globally, with an estimated prevalence rate of 10–20% [1,2]Most of the patients influenced with H. Pylori have no indications, but the contamination can lead to peptic ulcers, MALToma and adenocarcinoma of the stomach[2]. Incessant untreated reflux illnesses can cause a assortment of conditions counting esophagitis, Barrett's esophagus, esophageal carcinoma, gastric ulcers, and indeed life-threatening esophageal and gastric perfo-apportion [3–7]. The helpful administration of acid-related maladies and their complications have profoundly changed with the improvement of proton-pump inhibitors (PPIs). Since theiradvertise discharge within the late 1980s, PPIs spoken to the pillar for the treatment ofgastroesophageal reflux illness (GERD), peptic ulcer illness (PUD), low-dose headache medicine or non-steroidal antiinflammatory drug-induced peptic ulcer and Helicobacter pylori(H. pylori) infection.[8-10] The primary particle presented was omeprazole, taken after bylansoprazole, pantoprazole, rabeprazole and esomeprazole. Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) that belongs to a category of competitive potassium inhibitors. It functions by reversibly inhibiting the gastric acid pump through mechanisms that are competitive with potassium ions. In contrast to proton pump inhibitors (PPIs), which require acid activation for their action, P-CABs such as vonoprazan inhibit the enzyme via reversible ionic binding that competes with potassium. This results in vonoprazan providing rapid and sustained acid suppression, outperforming PPIs, which generally take about 3 to 5 days to reach their peak effect in gastric acid suppression.[11,12]

2. AIM AND OBJECTIVE

The objectives of Vonoprazan are:

1. To promote healing and reduce symptoms of erosive esophagitis.
2. To maintain healing and prevent relapse of erosive esophagitis.
3. To provide rapid and sustained relief from symptoms of gastroesophageal reflux disease (GERD), such as heartburn and regurgitation.
4. To promote healing of peptic ulcers.
5. To prevent recurrence of peptic ulcers.
6. To reduce gastric acid secretion and maintain a neutral pH in the stomach.

7. To improve patients' quality of life by reducing symptoms and complications associated with GERD and peptic ulcers.
8. To provide a new treatment option for patients who are intolerant or resistant to proton pump inhibitors (PPIs).

Vonoprazan

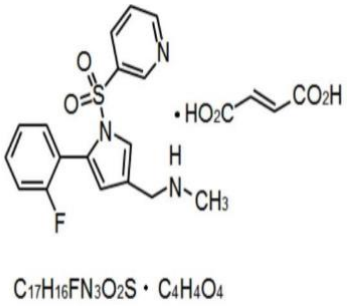

Fig no.1 structure of vonoprazan

3. MECHANISM OF ACTION

Vonoprazan is a P-CAB that reversibly binds to and blocks the H+, K+-ATPase enzyme, which is the gastric proton pump. This prevents the secretion of gastric acid. Vonoprazan, in contrast to PPIs, can provide quick and long-lasting acid suppression without the need for acid activation[13]. Unlike PPIs, vonoprazan reversibly inhibits H+ and K+-ATPase by competing with potassium ions. This is how its mechanism of action varies. On the other hand, PPIs affect the proton pump in an irreversible manner. With 350 times the potency of proton pump inhibitors, vonoprazan's reversible inhibition of H+, K+-ATPase activity reduces gastric acid secretion [13]. Compared to PPIs, vonoprazan acts faster and maintains acid suppression longer due to its reversible binding.

Furthermore, its capacity to obstruct the proton pump during its whole catalytic cycle without

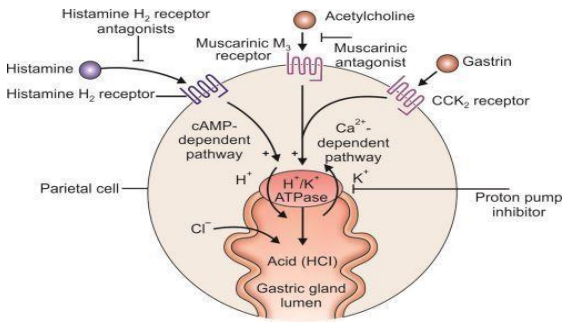

Fig no 2 mechanism of action vonoprazan

4. EFFICACY OF VONOPRAZAN

4.1. pre-clinical The antacid secretory effect of vonoprazan and lansoprazole was observed in the pig stomach through both in vitro and in vivo experiments. In an in vitro setting, the temperature was maintained at 37°C and the pH was maintained between 6 and 5. The inhibition of H+/K + ATPase was 400 times greater than that of lansoprazole. In the invivo setting, vonoprazan was 1.2– 2.0 times more powerful based on half fatal dose values. Vonoprazan is appropriate for usage in invitro and in-vivo settings, where the pH is neutral and extremely acidic, respectively, because it is not impacted by pH changes like lansoprazole is [14].

4.2 Clinical research –

GERD - It results from the stomach's acidic contents being rushed into the oesophagus, which can create issues like epithelium alterations. Although almost 30 to 40 percent of GERD patients are resistant to PPIs, they are the first-line treatment for the condition. A double-blind approach was used to observe the vonoprazan effect for the treatment of erosive oesophagitis. Following daily doses of 5, 10, 20, and 40 mg of vonoprazan and 30 mg of lansoprazole, 732 patients underwent endoscopic examinations. With vonoprazan 5, 10, 20, and 40 mg and 30 mg of lansoprazole, the healing proportions at week 4 were 92.3, 92.5, 94.4, 97.0, and 93.2, respectively. This indicates that vonoprazan is superior to lansoprazole in all of its actions [15].

ulcers- The effectiveness of vonoprazan versus esomeprazole in treating artificial ulcers following endoscopic submucosal dissection (post-ESD) was investigated in a number of randomised trials. The 92 patients in the P-2 group received 20 mg of vonoprazan and 20 mg of esomeprazole daily from the third day to the eighth week following ESD. According to endoscopic findings, vonoprazan caused ulcer constriction of 94.9%, compared to 78% with esomeprazole [16]. Another study that included 35 patients demonstrates the effectiveness of vonoprazan following ESD therapy for stomach adenoma. For four weeks, these 35 patients received 20 mg of vonoprazan daily. In contrast, 33 individuals received 20 mg of esomeprazole daily for the same amount of time. With an ulcer constriction rate of 97.7%, vonoprazan was much more effective than esomeprazole, which had a rate of 94.5% [17]

Helicobacter pylori elimination of Helicobacter pylori. In a randomised study involving 141 patients with apositive H. pylori history, the vonoprazan group's efficacy was noticeably higher. In IIT analysis, the eradication rate was 95.8 and 95% with the vonoprazan group (VPZ 20 mg, AMX 750 mg, and CLB 200–400 mg), but it was 69.6 and 95% with PPI [21]. 32 individuals with a history of erosive oesophagitis (EE) where administered 30 mg of lansoprazole and 20 mg of vonoprazan daily for 14 days in a randomised, double-blind research. Vonoprazan relieves heartburn sooner than lansoprazole does. On the first day, the reported rates for vonoprazan and lansoprazole were 31.3% and 12.5%, respectively. Well-tolerated were both regimens [50]. Patients with endoscopically confirmed EE participated in a double-blind parallel-group comparison research. Vonoprazan is not inferior to PPIs, as evidenced by the fact that, during an 8-week observation period, 99% of 401 patients were healed with vonoprazan and 95.5% with lansoprazole [18].

Gastric mucosal injury -

damage to the stomach mucosa. Eight patients with damage to their stomach mucosa took part of theinvestigation. They were already receiving regular PPI therapy and having their pH checked.
After therapy was stopped, the patients were reassessed, and they were then given 20 mg of vonoprazan daily. Patients tested negative for CYP2C19 metabolisers and H. pylori infection. Following vonoprazan therapy, full stomach mucosal healing occurs in 87.5% of patients (n = 7) [19].

Ulcer of stomach or duodenal ulcer
650 participants were permitted to participate in a double-blind, randomised trial. 641 of the 650 individuals got full first-time treatment. In first-line therapy, the eradication rate with vonoprazan was 92.6%, superior to the vonoprazan group by 16.7%, while the eradication rate with lansoprazole was 75.9%. Vonoprazan is therefore not less effective than PPIs. Well-tolerated were the first and second triple treatments [20].

Proton pump inhibitors and vonoprazan's relative effectiveness in various clinical trials.

Table no. 1

Reference	No of subjects	Disease	Dose of vonoprazan	Efficacy of vonoprazan	Efficacy of vonoprazan
K.ashida et al (2015) [15]	732	EE	5,10,20,mg	92.3–97%	93.2%
Tsuchiya et al. (2017)[16]	92	ESD	20mg	94.9%	78%
Maruoka et al. (2017) [17]	35	ESD artificalulcers	20mg	97.7%	94.5%
Masafumi Maruyama et al. (2017) [21]	141	H.pylori infection	20mg	95.8%	69.6%
Oshima et al. (2019) [22]	32	EE	20mg	31.3%	12.5%
Ashida et al. (2016) [20]	401	EE	20mg	99.0%	95.5%
Yamashita et al. (2017) [19]	8	Gastic mucosal injury	20mg	87.5%	NIL
Kazunari Murakami et al. (2016) [20]	650	Gastric or Doudental ulcer	20mg	92.6%	75.9%

5. SECURITY OR SAFETY

PPIs are the first line of treatment for GERD; however, recent studies have compared the safety and effectiveness of vonoprazan (20 mg daily) to PPIs, as well as the side effects. Vonoprazan and PPIs were directly compared in order to demonstrate that vonoprazan is not inferior to PPIs. PPI and vonoprazan have risk ratios of 1.08 and 1.06, respectively. Considering all of the negative consequences and effectiveness of both. Significantly, vonoprazan produced better results than lansoprazole; the RR value for vonoprazan was 1.14 (1.06–1.22). It implies that vonoprazan's safety outcomes are almost on par with those of PPIs, but with vonoprazan's higher efficacy [23]. Vonoprazan's effectiveness in eliminating H. pylori was compared to that of PPIs. A total of 14,636 patients were enrolled in this study. According to protocol analysis, the pooled ER of vonoprazancontaining regimens in first-line therapy was significantly greater than that of PPI-containing regimens (89.0%–774.2%). Vonoprazan produced significantly better results in the stains that were susceptible and resistant to

clariythromycin. Vonoprazan as a second-line treatment did not perform better than PPIs according to both the per-procedure analysis (89.3% vs. 90.1%) and intents to treat (83.4% vs. 82.0%). Ultimately, it was determined that the vonoprazan regimen was safer than PPI regimens (33.3% versus 26.4%). Safety is on par with or better than PPIs.[24]

6. ADVERSE EFFECTS

A randomized controlled trial was conducted on 2715 patients having 63-plus age. They were given VPZ and analyzed versus the old regimen i.e., PPIs. 10 cases of diarrhea were reported. 6 cases of nausea, and 5 cases of body rash were observed. All these adverse effects were normal and were also observed with PPIs in conventional use [25]. Adverse events were also studied in two groups in patients with Helicobacter pylori eradication. Both groups were given VPZ and PPIs and adverse effects were observed for a pre-decided duration. The first group consisted of 897 patients with H. pylori infection. Eradication rates with VPZ and PPIs were 91.4% and 74.5% respectively, while the adverse events came out to be 32.7% and 40.5% respectively in the first group, which indicates that VPZ has lesser adverse effects as compared to PPI while being more efficacious [26]. The other group had 141 patients with H. pylori infection. The adverse effects in this group came out to be 26.3% and 37.7% for VPZ and PPIs respectively. Eradication rates were 95.8% and 69.6% with VPZ and PPIs, respectively [21]

Comparing the Side Effects of PPIs and VPZ in the Eradication of Helicobacter pylori.

Table no 2

No with patients	Disrase	ER VPZ	ER PPIs	Adverse events VPZ	PPIs	References
897	H.pylori eradication	91.4%	74.8%	32.7%	40.5%	Qiu-Ju Lyu et al. (2019) [26]
141	H.pylori eradication	95.8%	74.8%	26.3%	37.7%	Masafumi Maruyama et al. (2017) [21]

7. COST EFFECTIVENESS

Cost-effectiveness In Japan, 20 mg of Vonoprazan and 30 mg of Lansoprazole therapy were used to treat reflux oesophagitis, and the cost-effectiveness of the treatment was examined over a 12-month period. According to studies, VPZ was more cost-effective than lansoprazole, costing 58 yen per day as opposed to 68 yen per day, respectively [27]. The remission rate of erosive oesophagitis was examined in another cost-effectiveness analysis that took treatment costs into account. Lansoprazole-based intermittent PPI therapy costs 39 yen per day, whereas vonoprazan-based intermittent P-CAB therapy also costs 39 yen per day. Although Vonoprazan maintenance therapy is more successful for reflux oesophagitis, it costs 185 yen per day, whereas using a PPI for maintenance therapy costs 122 yen per day. [28]Rabeprazole triple therapy was used to eradicate Helicobacter, and the overall cost was compared to Vonoprazan triple therapy. Amoxicillin, Clarithromycin, and VPZ or RPZ were used as triple treatment. This retrospective investigation was conducted on 209 patients in Yasaku, Japan. Vonoprazan triple therapy and Rabeprazole triple therapy were found to have cost-effective ratios of 360.1 and 379.4 Japanese yen, respectively [28].

Cost-effectiveness comparison between PPIs and VPZ.

Table no 3

Disease	CEO of VPZ	CER of PPI's	References
Reflux esophagitis	58 YEN/DAY	68 YEN/DAY	Habu et al. (2019) [27].
Reflux esophagitis	31 YEN/DAY	39 YEN/DAY	Yasuku Habu et al. (2021) [28]

8. PHARMACOLOG OF VONOPRAZAN

8.1.Vanoprazan's Pharmacokinetic Characteristics

The pharmacokinetics of vonoprazan are independent of time [29,30]. Vonoprazan is quickly absorbed after oral treatment, reaching peak plasma concentrations 1-3 hours after dosage.

Vonoprazan exposure is about dose-proportional over the dose range of 10–40 mg, with steady-state concentrations attained by days 3–4 [29, 30], according to clinical trials including once-daily dosing in healthy participants. Vonoprazan's pharmacokinetics are not clinically affected by meals [31], and it is possible to take the medication without considering food [32,29]. The mean steady-state plasma exposure is almost 1.8 times more than on day 1 when vonoprazan 20 mg is taken twice daily [29]. Vonoprazan has an apparent oral volume of distribution of 782.7 L when taken twice daily at steady state. Vonoprazan's affinity to plasma proteins is around 85to88% [29]

According to in vitro research, CYP3A4 is the primary mediator of vonoprazan metabolism, with sulfo- and glucuronosyl-transferases, CYP2B6, CYP2C9, CYP2C19, and CYP2D6 also playing a role [29, 33]. The elimination half-life of vonoprazan is around seven hours [29]. With twice-daily dosage, the apparent oral clearance at steady state is 81.3 L/h. About 67% and 31% of a radiolabeled dosage of vonoprazan, respectively, were found in urine and faeces after oral treatment, primarily as metabolites [29]. Vonoprazan pharmacokinetics did not differ clinically significantly by sex, age (less than 65 years against more than 65 years), race (Asian versus nonAsian), or CYP2C19 metaboliser status [29, 30, 34, 35].

8.2.Vanoprazan's Pharmacodynamic Characteristics -

The stomach proton pump H +/K+-ATPase is strongly inhibited by vonoprazan [29, 36]. It blocks potassium binding by competitively inhibiting its noncovalent and reversible binding to H +/K+ATPase. By doing this, vonoprazan raises the intragastric pH by quickly, significantly, and persistently suppressing the production of gastric acid [30]. Antibacterials used to treat H. pylori infections are more stable when the intragastric pH rises [37, 32]. Furthermore, the increased intragastric pH aids in the replication of H. pylori bacteria, making them more vulnerable to antibacterial treatments that depend on active bacterial growth for maximum efficacy [32,38] The pharmacodynamic findings from the UK and Japanese trials were comparable. Intragastric pH elevations began quickly (two to three hours after the first dosage) and persisted for the full 24-hour dosing interval. The mean 24-hour intragastric pH > 5 holding time ratios (HTRs) on day 7 with 20 mg and 40 mg of vonoprazan, respectively, were 78.6% and 85.0% in the UK study and 73.2% and 98.6% in the Japanese study. Additionally, the Japanese trial showed mean nighttime pH > 5 HTRs on day 7 with the corresponding doses of 55.9% and 97.2%, while the UK study showed mean nighttime pH > 5 HTRs of 66.9% and 77.5% [ref18]. The 24-hour intragastric pH > 6 HTR on day 7 was significantly ($p < 0.0001$) higher in a different study with healthy US participants. greater with 20 mg of vonoprazan once daily (62.5%) compared to 16.4% with 30 mg of lansoprazole once daily. [39]

9. DOSAGE AND HOW TO TAKE IT

Vonoprazan comes in two forms: film-coated tablets in 10 mg and 20 mg doses. The suggested amount to treat erosive esophagitis is 20 mg once a day for a period of eight weeks. It is advised to take 10 mg once a day for six months to sustain the healing process. Vonoprazan is used in combination with antibiotics for treating H. pylori infection. The suggested treatment for dual therapy consists of taking 20 mg twice a day along with amoxicillin 1,000 mg three times a day for 14 days. The triple therapy regimen consists of 20 mg of vonoprazan taken twice a day along with amoxicillin 1,000 mg three times a day and clarithromycin 500 mg twice a day for a duration of 14 days [40]. Vonoprazan can be consumed with or without a meal, and remember to swallow the pills whole without biting or smashing them. If a dose is not taken as scheduled, special directions are given depending on the reason and how much time has passed since missing the dose. Vonoprazan's pharmacokinetics display consistent behavior not influenced by time, with steady-state levels usually achieved after 3-4 days of dosing. The elimination half-life of Vonoprazan falls within the range of 6.8 to 7.9 hours, with its main routes of elimination being through urine (67%) and feces (31%) [41].

10. USE IN VARIOUS AGE GROUPS

Patient demographics and unique factors Utilisation in Various Age Groups Vonoprazan's effectiveness and safety in a range of clinical settings have been

evaluated in a variety of age groups. For patients under 50, the vonoprazan group had a much better success rate (92.6%) than the PPI group (67.8%) in studies comparing the two medications for primary eradication therapy. Vonoprazan also shown better, though less noticeable, success rates among patients over 50, with 90.2% success rates compared to 74.3% for PPIs [42]. The superiority seen in younger patients did not translate well when vonoprazan-based triple therapy was examined in individuals over 60, indicating possible variations in efficacy in the older population [43]. The safety profile of vonoprazan was generally comparable to PPIs, with similar rates of treatmentemergent AEs observed across age groups. Specific adverse effects unique to vonoprazan were not identified, and its efficacy remained consistent across the age spectrum compared to PPIs. Furthermore, ongoing research includes a Phase 1 clinical trial recruiting children aged six to 11 years to evaluate the pharmacokinetics, pharmacodynamics, and safety of vonoprazan in treating GERD. This study aims to provide crucial insights into the safety and efficacy of vonoprazan in a younger age group that has not been extensively studied previously [44].

11. CONSIDERATIONS FOR PATIENTS WITH COMORBID CONDITIONS

P-CAB vonoprazan has demonstrated superiority over PPIs in the treatment of a number of disorders related to gastric acid while remaining non-inferior in others. For example, compared to PPI-based regimens, vonoprazan-based regimens produce significantly higher eradication rates for first-line H. pylori eradication (89.0%-97.4% vs. 69.6%-82.0%). Additionally, it works better than lansoprazole in the treatment of gastric/duodenal ulcers (eradication rates of 92.6% vs. 75.9%) and erosive oesophagitis (healing rates of 92.3%-99.0% vs. 93.2%-95.5%). Furthermore, vonoprazan has a 94.9% healing rate for post-ESD ulcers, which is higher than the 78% healing rate for PPIs [45].Vonoprazan's safety profile is mostly similar to that of PPIs, with comparable incidence of treatment-emergent adverse events (AEs) (33.3% vs. 26.4%). However, because of its strong and long-lasting acid suppression, which may result in hypergastrinemia, there are worries about possible longer-term safety risks. Due to the paucity of safety evidence in this population, patients with duodenal ulcers should be prescribed vonoprazan with extra caution [46]. The pharmacokinetics and effectiveness of vonoprazan are consistent in both Asian and non-Asian individuals. Although it is more effective than PPIs for a number of diseases, such as erosive oesophagitis, gastric/duodenal ulcers, and post-ESD ulcers, patients with duodenal ulcers should be carefully evaluated because of the paucity of safety evidence [47].

12. GUIDELINES AND RECOMMENDATIONS FOR CLINICIANS

The first line of treatment for severe reflux oesophagitis is vonoprazan. Vonoprazan is suggested as a maintenance medication, but both PPIs and vonoprazan are appropriate first therapies for mild patients. In Japan, 10 mg of vonoprazan is taken daily as maintenance treatment to stop recurrence of erosive reflux disease. Vonoprazan-based triple therapy (20 mg twice daily with amoxicillin 1,000 mg three times daily with clarithromycin 500 mg twice daily) and dual therapy (20 mg twice daily with amoxicillin 1,000 mg three times daily) are advised for the treatment of H. pylori infection [48].With an elimination half-life of 6.8 to 7.9 hours, vonoprazan demonstrates timeindependent pharmacokinetics, reaching steady-state concentrations by days 3–4 of treatment. Due to the paucity of safety evidence in this population, vonoprazan use in patients with duodenal ulcers should be done with caution. Monitoring is necessary for long-term safety concerns such as hypergastrinemia and the possible emergence of endocrine cell tumours. In the treatment of erosive oesophagitis and first-line H. pylori eradication, vonoprazan outperforms PPIs; nevertheless, it is not inferior in other conditions linked to stomach acid. To prove comparable safety and efficacy with different P-CABs, more investigation is necessary [49].The American Gastroenterological Association's guidelines advise avoiding taking more calcium, vitamin B, or other supplements because of possible safety issues with PPIs. When administering vonoprazan, clinicians should closely follow patients and take possible long-term safety concerns into account [40]

13. CONCLUSION

This review article shows that venoprazan is 400 times better than the use of PPIs tested in preclinical studies because it does not affect pH changes. We also demonstrated that VPZ is more effective than clinical trials conducted with VPZ for GERD, esophagitis and gastric or duodenal ulcers. This article shows that although it is better, the safety

profile of vonoprazan in reflux gastritis is similar to the use of PPI, there is no significant clinical difference in safety. However, the evidence suggests that in the case of H. PPI. Our article shows that VPZ is worth more than PPI. But we also explained that the use of P-CAB is more cost-effective in patients with reflux esophagitis and Helicobacter pylori cation. But a more effective strategy for the treatment of esophageal reflux is to continue the maintenance dose of PPI or P-CAB, which is more cost effective with P-CAB than PPI..

14. REFERENCES

[1] J. Dent, H.B. El-Serag, M. Wallander, S. Johansson, Epidemiology of gastrooesophageal reflux disease: a systematic review, Gut 54 (5) (2005 May 1) 710–717.

[2] 2B.B. de Brito, F.A.F. da Silva, A.S. Soares, V.A. Pereira, M.L.C. Santos, M. M. Sampaio, P.H.M. Never F.F. de Melo, Pathogenesis and clinical management of Helicobacter pylori gastric infection, World J. Gastroenterol. 25 (37) (2019 Oct 7) 5578–5589.

[3] S.J. Spechler, R.K. Goyal, Barrett's esophagus, N. Engl. J. Med. 315 (6) (1986 Aug 7) 362–371.

[4] A.C. Ford, D. Forman, R.H. Hunt, Y. Yuan, P. Moayyedi, Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials, Br. Med. J. (2014 May 20) 348

[5] K. Fukase, M. Kato, S. Kikuchi, K. Inoue, N. Uemura, S. Okamoto, S. Terao, K. Amagai, S.Hayashi, M. Asaka, Japan Gast Study Group, Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial, Lancet 372 (9636) (2008 Aug 2) 392– 397.

[6] S.B. Yoon, J.M. Park, C.H. Lim, Y.K. Cho, M.G. Choi, Effect of Helicobacter pylori eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis, Helicobacter 19 (4) (2014 Aug) 243–248.

[7] A.C. Ford, B. Delaney, D. Forman, P. Moayyedi, Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients, Cochrane Database Syst. Rev.(2)(2006).

[8] Martinucci I, Blandizzi C, Bodini G, et al. Vonoprazan fumarate forthe management of acid relateddiseases.ExpertOpinPharmacother.2017;18(11):11451152doi:10.1080/14656566.2017.1346087

[9] Savarino V, Marabotto E, Zentilin P, et al. Proton pump inhibitors: useand misuse in the clinical setting. Expert Rev Clin Pharmacol. 2018;11(11):1123–1134.

[10] Savarino V, Dulbecco P, de Bortoli N, Ottonello A, Savarino E. Theappropriate use of proton pump inhibitors (PPIs): need for areappraisal.Eur J Intern Med.2017;37:19–24. doi:10.1016/j.Ejim.2016.10.007

[11] Jenkins, H.; Sakurai, Y.; Nishimura, A.; Okamoto, H.; Hibberd, M.; Jenkins, R.; Yoneyama, T.; Ashida, K.; Ogama, Y.; Warrington,S. Randomised Clinical Trial: Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Repeated Doses of TAK-438(Vonoprazan), a Novel Potassium-Competitive Acid Blocker, in Healthy Male Subjects. Aliment. Pharmacol. Ther. 2015, 41, 636–648.[CrossRef] [PubMed]

[12] .Oshima, T.; Miwa, H. Potent Potassium-Competitive Acid Blockers: A New Era for the Treatment of Acid-Related Diseases. J.Neurogastroenterol. Motil. 2018, 24, 334–344.

[13] Rawla P, Sunkara T, Ofosu A, Gaduputi V: Potassium-competitive acid blockers-are they the next generation of proton pump inhibitors?. World J Gastrointest Pharmacol Ther. 2018, 9:63-8.

[14] X.Y.-Q. Li, Vonoprazan; A novel and potent alternative in the treatment of acid related diseases, Dig. Dis.Sci.(2017).

[15] K. Ashida, S. Y, Randomized clinical trial; a dose-ranging study of vonoprazan, anovel potassium-competitive acid blocker, vs lansoprazole for the treatment oferosive esophagitis, Aliment Pharmacol. Therapeut.(2015)685–695.

[16] L.Tsuchiya, Effect of vonoprazan on the treatment of artificial gastric ulcers afterendoscopic submucosal dissection; prospective randomized controlled trial,National Library of Medicine (2017).

[17] D. Maruoka, Vonoprazan is superior to proton pump inhibitors in healing artificial ulcers of stomach post-endoscopic submucosal dissection; A propensity scorematching analysis, National Library of Medicine (2017)

[18] K. Ashida, Randomized clinical trial; vonoprazan, a novel potassium competitive acid blocker, vs. lansoprazole for the healing of erosive esophagitis, National Library of Medicine (2016).

[19] H. Yamashita, The effects of switching to vonoprazan, a novel competitive acid blocker, on gastric acidity and reflux patterns in patients with erosive esophagitis refractory to proton pump inhibitors, National Library of Medicine (2017).

[20] Y.S. Kazunari Murakami, Vonoprazan, a novel potassium competitive acid blocker,as a component of the first-line and second-line triple therapy for Helicobacter pylori eradication; a phase 3, randomized double-blind study, Gut (2016) 1439–1446.

[21] N.T. Masafumi Maruyama, The vonoprazan-based regimen is more useful than the PPIbased one for first-line Helicobacter pylori eradication; A Randomized Controlled Trial. Canadian, J. Gastroenterol. Hepatol. (2017).

[22] K. Ashida, Randomized clinical trial; vonoprazan, a novel potassium competitive acid blocker, vs. lansoprazole for the healing of erosive esophagitis, National Library of Medicine (2016).

[23] Cheng Y. Direct comparison of the efficacy and safety of vonoprazan versus proton pump inhibitors for gastroesophageal reflux disease; a systemic review and meta-analysis. National Library of Medicine. 2021

[24] Dong S.Q. Review; A Japanese population-based meta-analysis of von Drazan versus PPI for Helicobacter pylori eradication therapy; Is superiority an illusion/ National Library of Medicine. 2017

[25] S. Shichijo, Vonoprazan versus conventional proton pump inhibitor-based triple therapy as first-line treatment against Helicobacter pylori; A multicenter retrospective study in clinical practice, National Library of Medicine (2016)

[26] Q.-H.P.-F. Qiu-Ju Lyu, Efficacy and safety of vonoprazan-based versus proton pump inhibitor-based triple therapy for Helicobacter pylori eradication; A meta- analysis of randomized clinical trials, BioMed Res. Int. (2019)

[27]]Habu Y. Vonoprazan versus Lansoprazole for the initial treatment of Reflux Esophagitis; A cost-effectiveness analysis in Japan. National Library of Medicine. 2019

[28] Yasuku Habu R.H. Treatment strategies for reflux esophagitis including a potassiumcompetitive acid blocker; A cost-effectiveness analysis in Japan. Journal of General and Family Medicine. 2021

[29] Phathom Pharmaceuticals Inc. Voquezna (vonoprazan) tablets: US prescribing information. 2023.https://www.phathompharma.com/wp-content/uploads/VOQUEZNA-tabletsPrescriber-Information.pdf. Accessed 19 Dec 2023.

[30] Jenkins H, Sakurai Y, Nishimura A, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Phar-macol Ther. 2015;41(7):636–48

[31] Mulford DJ, Leifke E, Hibberd M, et al. The efect of food on the pharmacokinetics of the potassium-competitive acid blocker vonoprazan. Clin Pharmacol Drug Dev. 2022;11(2):278–84.

[32] Phathom Pharmaceuticals Inc. Voquezna Triple Pak (vono-prazan tablets; amoxicillin capsules; clarithromycin tablets) and Voquezna Dual Pak (vonoprazan tablets; amoxicillin capsules):US prescribing information. 2023. https://www.phathompharma.com/wp content/uploads/VOQUEZNA-TRIPLE-PAK-and-VOQUEZNA-DUAL-PAK-FDA-Final-Label-3.pdf. Accessed 19 Dec 2023.

[33] Yamasaki H, Kawaguchi N, Nonaka M, et al. In vitro metabolism of TAK-438, vonoprazan fumarate, a novel potassium-competitive acid blocker. Xenobiotica. 2017;47(12):1027–34.

[34] Sakurai Y, Nishimura A, Kennedy G, et al. Safety, tolerabil-ity, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (vonoprazan) doses in healthy male Japanese/non-Jap anese subjects. Clin Transl Gastroenterol. 2015;6(6): e94.

[35] Scarpignato C, Leifke E, Smith N, et al. A population pharma-cokinetic model of

vonoprazan: evaluating the efects of race, disease status, and other covariates on exposure. J Clin Pharmacol.2022;62(6):801–11.

[36] Shin JM, Inatomi N, Munson K, et al. Characterization of a novel potassium-competitive acid blocker of the gastric H, K-ATPase, 1-[5-(2-fuorophenyl)-1-(pyridin-3-ylsulfonyl)-1Hpyrrol-3-yl]- N-methylmethanamine monofumarate (TAK-438). J Pharmacol Exp Ther. 2011;339(2):412–20.

[37] Scott DR, Sachs G, Marcus EA. The role of acid inhibition in Helicobacter pylori eradication. F1000Res. 2016;5(F1000 Faculty Rev):1747.

[38] Marcus EA, Inatomi N, Nagami GT, et al. The efects of varying acidity on Helicobacter pylori growth and the bactericidal efcacy of ampicillin. Aliment Pharmacol Ther. 2012;36(10):972–9.

[39] Laine L, Sharma P, Mulford DJ, et al. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan and the proton pump inhibitor lansoprazole in US subjects. Am J Gastroenterol. 2022;117(7):1158–61.

[40] Voquezna (vonoprazan) dosing, indications, interactions, adverse effects, and more. (2024). Accessed: July 9, 2024:https://reference.medscape.com/drug/voquezna-vonoprazan4000266.

[41] Vonoprazan(oralroute).(2024).Accessed:July9 2024: https://www.mayoclinic.org/drugssupplements/vonoprazan-oral-route/proper-use/drg-20559712.

[42] Abbasi A, Siddiqui SA, Ram B, et al.: Real-world evidence to evaluate the efficacy and safety of vonoprazan in gastrointestinal disorders in the pakistani population. Cureus. 2023

[43] Kusunoki M, Yuki M, Ishitobi H, et al.: Effect of age on effectiveness of vonoprazan in triple therapy for Helicobacter pylori eradication. Intern Med. 2019, 58:1549-55. 10.2169/internalmedicine.2233-18

[44] Miao J, Hu C, Tang J, et al.: Pharmacokinetics, safety, and tolerability of vonoprazan-or esomeprazole-based bismuth-containing quadruple therapy: a phase 1, double-blind, parallel-group study in adults with Helicobacter pylori infection in China. Clin Pharmacol Drug Dev. 2023, 12:1036-44. 10.1002/cpdd.1276

[45] Simadibrata DM, Syam AF, Lee YY: A comparison of efficacy and safety of potassiumcompetitive acid blocker and proton pump inhibitor in gastric acid-related diseases: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2022, 37:2217-28. 10.1111/jgh.16017

[46] Shehryar M, Ahmad RU, Kareem HK, et al.: Efficacy, safety and cost-effectiveness of vonoprazan vs Proton Pump Inhibitors in reflux disorders and H. pylori eradication: a literature review. Ann Med Surg (Lond). 2022,

[47] Zhang M, Xiao Y, Chen M: The role of vonoprazan in patients with erosive esophagitis. Therap Adv Gastroenterol. 2022, 15:10.1177/17562848221122623

[48] Goth Y, Ishibashi E, Honda S, Nakaya T, Noguchi C, Kagawa K, Murakami K: Efficacy of vonoprazan for initial and maintenance therapy in reflux esophagitis, nonerosive esophagitis, and proton pump inhibitor-resistant gastroesophageal reflux disease. Medicine (Baltimore). 2020, 99:e19520. 10.1097/MD.0000000000019520

[49] Moraes-Filho JP, Domingues G, Chinzon D, Guedes JL, Santos CY, Zaterka S: Vonoprazan in the management of gastric/peptic ulcers: a systematic review of safety data. Prz Gastroenterol. 2022, 17:266-73. 10.5114/pg.2022.112777

[50] T. Oshima, Randomized clinical trial; vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive esophagitis, National Library of Medicine (2019).