Chapter

Vonoprazan Versus Conventional Proton Pump Inhibitor in the Therapeutic Armamentarium of Peptic Ulcer Disease and Gastroesophageal Reflux Disease

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Abstract

Vonoprazan is a novel potassium-competitive acid blocker that has been introduced as an effective treatment option in peptic ulcer and gastroesophageal reflux diseases. Its adverse events panel is encouraging compared to standard proton pump inhibitors, although higher hypergastrinemia and foveolar-type gastric adenocarcinoma occurrence have been described. The efficiency is proved in gastric and duodenal ulcer, gastroesophageal reflux and gastric post- endoscopic submucosal dissection ulcers, with higher ulcer shrinkage rate and no incremental risk for bleeding. The new therapies containing Vonoprazan instead of convention proton pump inhibitors against Helicobacter pylori are safe and well-tolerated, being associated with a better eradication rate. However, the therapy should be adjusted to the body size.

Keywords: Vonoprazan, Helicobacter pylori, peptic ulcer, proton pump inhibitors, gastroesophageal reflux

1. Introduction

Vonoprazan is part of the potassium competitive acid blockers (P-CABs) family that has been reported as being effective against a range of stomach acid related conditions due to its acid suppressant activity. It activates on the final step of the acid secretion pathway, more specifically on the gastric H+/K + -ATPase proton pump. Due to its effects as an acid suppressor, vonoprazan is reported as being useful in preventing acid-related injuries due to excessive acid exposure. Pathologies, where such effects may prove useful, include gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD) as well as infections with *Helicobacter Pylori* [1].

2. Methodology

We performed an extensive search of PubMed using the following terms: vonoprazan, ulcer peptic disease, gastroesophageal reflux disease, Helicobacter

pylori, NSAIDs, submucosal dissection limited to randomized controlled trials, multicenter studies, observational studies, and controlled or uncontrolled clinical trials. We applied filters for the English language and for the adult population.

3. Drug comparison

Vonoprazan, unavailable in Europe and USA, is classed as P-CABs that selectively bind to the E2-P conformation of H+/K + -ATPase inhibit K + -stimulated acid secretion by competing with K+ in binding to E2-P. Together with proton pump inhibitors (PPI) are the drugs used to treat acid-related diseases because of their inhibiting action on H+/K + -ATPase. There are several differences in behavior and characteristics between these two drug categories. Vonoprazan has an ionic and reversible binding method which is different from the covalent and irreversible binding of proton pump inhibitors (PPI). It can link with H+/K + -ATPase in both active and rest phases, meanwhile, the PPIs act only on the active phase. It is also acid-stable, unlike PPIs, and it has a greater half-life (9 hours) as opposed to PPIs (0.5–2.1 hours). Its potency of inhibition is 350 times higher than lansoprazole.

Vonoprazan is absorbed rapidly and reaches maximum plasma concentration at 1.5–2.0 h after oral administration. Food has minimal effect on its intestinal absorption. The mean apparent terminal half-life of the drug is approximately 7.7 h in healthy adults. Vonoprazan is metabolized to inactive metabolites mainly by cytochrome P4502. The plasma protein binding of vonoprazan is 80% in healthy subjects. It distributes extensively into tissues with a mean apparent volume of distribution of 1050 L. This aids in vonoprazan's greater ease of use because it only requires only one administration to be effective and it is also flexible in its administration time, allowing for after meal administration in contrast to PPIs which require not only repeated administration but also strict before meal administration. It has also been observed that Vonoprazan administration leads to a significantly higher pH value (9.06) than PPIs (3.8–5.0). There is no correlation observed between median intragastric pH and CYP2C19 genotypes [1].

4. Role of vonoprazan in gastric/duodenal ulcer

Because vonoprazan elicited a more extensive gastric acid suppression than the proton pump inhibitor, lansoprazole, it also gave rise to two to three times greater serum gastrin concentrations as compared with lansoprazole. During repeated dosing of 20 mg once daily, the 24-h intragastric pH >4 holding time ratios were 63 and 83% on days 1 and 7, respectively [2]. Vonoprazan is recommended by Japanese guidelines for healing gastric /duodenal ulcer as an alternative to PPI, both being superior to anti H2 treatment [3].

5. Efficiency in use for post-endoscopic submucosal dissection (ESD) ulcers

5.1 Vonoprazan vs. esomeprazole

The first study that is to be discussed is a controlled test between a mix of Vonoprazan versus Esomeprazole in treating ESD-induced ulcers. Esomeprazole is a PPI, that is reported to have shown greater inhibitory action than other PPIs. This

study used patients who had undergone ESD for gastric neoplasm and excluded and who were either allergic to the medicine or had a severe heart or liver disfunction. The *H. pylori* patients received eradication therapy after the trial.

Out of a total of 84 patients, 40 were randomly assigned to the 20 mg Esomeprazole group and 44 to the 20 mg Vonoprazan group. Two patients could not complete the study, so the analysis was based on the remaining 43 patients in the Vonoprazan group and the 39 in the Esomeprazole group.

In the end, this study yielded no significant results that confirmed a difference between the two treatment options. At 4 weeks, the Vonoprazan group had an ulcer scar rate of 20.9% and a size reduction rate of 94.6%. Meanwhile, the Esomeprazole group had an ulcer scar rate of 15.4% and a size reduction rate of 93.8%. At the 8-week point, the ulcer scar rate for the Vonoprazan group was 90.7% and 92.3% for the Esomeprazole group. The ulcer reduction rates were 99.7% for the Vonoprazan group and 99.3% for the Esomeprazole group.

Delayed bleeding occurred in one patient from the Vonoprazan group and 4 of the Esomeprazole group (2.33% and 10.2%, respectively). No perforations occurred in either group and while there was one case of Mallory-Weiss syndrome in the Esomeprazole group and one case of acute myocardial infarction in the Vonoprazan group, the incidence of these conditions poses no statistical difference between the two drugs. As well as that, no adverse effects regarding the drugs used in the study were observed [4].

5.2 *Vonoprazan* vs. *lansoprazole*

The study drew patients from a population of Japanese natives treated with gastric neoplasm by use of ESD. They were then randomly distributed across two groups that were to be treated either with vonoprazan 20 mg (61 patients-V groups) or lansoprazole 30 mg (66 patients- L group).

The healing ratio at 4 and 8 weeks did not differ significantly between the V and L groups was statistically insignificant.

Delayed bleeding was observed in both groups of patients with no statistical difference between them. Perforation was observed in one patient from the V group and two patients from the L group [5].

Other randomized controlled trial on 216 patients evaluated the healing effects of vonoprazan and lansoprazole on ESD-induced ulcers. Again, there were no significant differences in the reduction rate of ulcers between the vonoprazan and lansoprazole groups at 4 weeks, 94.0 vs. 93.4% or 8 weeks, 99.8 vs. 99.9% [6].

5.3 *Vonoprazan* vs. *Rabeprazole*

From 190 patients who underwent ESD, there were 167 enrolled in the study, being split into a Rabeprazole group (n = 90), which received 20 mg rabeprazole orally once per day, and a V group (n = 77) which received 20 mg vonoprazan orally once per day.

The efficiency evaluation was done based on the healing ratio between vonoprazan and rabeprazole groups as well as the scarring ratio between the two groups.

The scarring rates of all lesions were not significantly different between the vonoprazan and rabeprazole groups (31.7 vs. 18.9%; $p = 0.07$). There were exceptions for lesions with a diameter ≤ 35 mm. For this category scarring rate in the vonoprazan group was superior to that in the rabeprazole group (42.2 vs. 19.2%; $p < 0.05$). This was also the case for ulcers with a surface lesser than 3–100 mm2, for which scarring rate in the vonoprazan group also was superior to that in the rabeprazole group (48.7 vs. 20.0%; $p < 0.05$).

Overall, the reduction rate for all lesions was superior in the V group (93.0 vs. 90.4%; $p < 0.05$), being distributed similarly to the scarring rates, meaning that lesions under 35 mm in diameter and 3–100 mm^2 are shown to have superior healing times in the V group than in the R group. However, for those lesions greater than these, there have been no statistical differences in the reduction rates between groups.

It was also found that Vonoprazan is superior to Rabeprazole for compete for ulcer scarring (OR 2.21; 95% CI 1.03–4.71; $p < 0.05$), therefore reducing the risk of incomplete scarring for large lesions.

Further complications, such as delayed bleeding were found in both groups, but their distribution was statistically insignificant [7].

A meta-analysis study including (5 studies, 2 abstracts) patient's healing rates at 4 and 8 weeks post-ESD was conducted in the early days of Vonoprazan's introduction in Japan had shown that a 20 mg Vonoprazan dose had similar treatment efficiency to standard PPI based treatment schemes [8].

Later on, another meta-analysis study was performed, also utilizing studies based on Japanese subjects, which showed significant results when comparing Vonoprazan with other PPI based treatments. In the end, six studies were selected. Initial results at a period between 4 and 8 weeks post ESD showed that the OR for complete healing in patients treated with Vonoprazan stood at 2.27 when compared with patients treated with PPIs. The statistical heterogeneity was insignificant, with an I2 of 0%. Subgroup analysis based on the time of repeated upper endoscopy yielded a significantly higher rate of completely healed ulcers in both the 4-week and the 8-week subgroup, with pooled ORs of 2.21 and 2.40, respectively. This meta-analysis has also shown that while the OR (0.79) of adverse effects is numerically lower for vonoprazan than PPI, statistical analysis has not been shown to be statistically relevant [9].

Another meta-analysis on 1328 patients showed a potential superiority on reducing the risk of post-ESD bleeding compared with PPIs, with a pooled OR of 0.69, although there was no statistically significant difference, with a higher scar formation rate OR = 1.58 [10]. Therefore, it is conclusive to state that Vonoprazan is a superior treatment method in case of post-ESD ulcers, especially in the first 2 weeks of treatment [11] and its side effects are no more severe than other PPI based treatments [12].

The bleeding rate in post ESD 1715 patients was lower for vonoprazan than PPI with an overall bleeding: 11.9% vs. 17.2%, $p = 0.008$; bleeding between days 2 and 30: 7.8% vs. 11.8%, $p = 0.015$ and readmission rate for bleeding 2.4% vs. 4.1%, $p = 0.081$ in a retrospective study [13]. A prospective multicentric Japanese study showed that the rate of delayed bleeding in the Vonoprazan and PPI groups was 3.9 and 4.4%, respectively with non-inferiority for the scar-stage ulcer at 6 weeks in the Vonoprazan group and 8 weeks in the PPI group was 68.3 and 74.6%, respectively ($p = 0.19$) [14].

6. Vonoprazan in the treatment of *H. pylori*

The triple therapy using PPI/amoxicillin/metronidazole or PPI/amoxicillin/clarithromycine or PPI based quadruple (bismuth salt/tetracycline/nitro-imidazol) is associated with an 80–92% eradication rate [3]. The association of Vonoprazan with different antibiotics for HP eradication showed a high rate of eradication (97%) and in the patients who had prior treatments for HP, the non- vonoprazan therapy was associated with a lower eradication rate (91%) [15]. A multicentric randomized study proved that the 7-day vonoprazan and low-dose amoxicillin

dual therapy provided acceptable *H. pylori* eradication rates and a similar effect to vonoprazan-based triple therapy in regions with high clarithromycin resistance (eradication rate of 84.5% and 89.2%) [16]. A recent meta-analysis showed that the best results for HP eradication were obtained with vonoprazan triple therapy, over 90%, and the standard triple therapy had the lowest results [17]. The recommendation of the 2020 guideline sustains the use of vonoprazan as first line therapy, using antibiotics such as amoxicillin, clarithromycin, or metronidazole [3]. When PPI is used as first-line therapy, the indication is to use quadruple therapy or sequential therapy [18]. For the second-line therapy, the association of PPI or Vonoprazan with amoxyciline and metrondazol is recommended [3]. Also, the incidence of adverse events in vonoprazan-based triple therapy was lower than that in PPI-based triple therapy (pooled incidence, 32.7% vs. 40.5% [19].

Successful H. pylori eradication with vonoprazan- amoxicillin dual therapy was associated with the small body size of patients (eradication rate: 90.8% in patients with body surface area < 1.723 vs. 79.6% in those with body surface area ≥ 1.723; $p = 0.045$). This showed that vonoprazan therapy should be adjusted to body size [20].

The impact of the therapy of eradication based on Vonoprazan was studied in 43 patients in association with Amoxicillin or Amoxicylin/ Claritromicine. One year assessment of gut microbiota was modified qualitatively and quantitatively and correlations with the bodyweight were found [21].

7. Drug-induced ulcers

Vonoprazan is not recommended yet for treating ulcers that occurred after NSAIDS when the interruption of NSAIDs and association with PPI is considered, but they are recommended for their prevention [3].

7.1 Ulcer recurrence prevention during long term NSAID therapy

Those patients that receive NSAID treatment for chronic illnesses to manage inflammatory symptoms have been found to have a risk of ulcers as high as 62%. The current solution for patients that need this treatment is to prescribe acid blockers alongside the treatment.

One randomized controlled study compared Lansoprazol 15 mg with Vonoprazan 10 mg and 20 mg in patients under NSAIDs treatment but with no history of ulcer.

There were non-inferiority effects of Vonoprazan 10 mg and 20 mg when compared to the lansoprazole 15 mg group. Recurrent peptic ulcers within 24 weeks on endoscopy assessment were lower for the vonoprazan 10 mg (3.3%) and 20 mg (3.4%) groups compared with the lansoprazole 15 mg group (5.5%). The non-inferiority effect of vonoprazan 10 mg and 20 mg to lansoprazole was verified because the percentage difference between treatment groups was <8.3% (percentage difference − 2.2%, $p < 0.001$; −2.1%, $p < 0.001$, respectively). Tolerability was not apparent to be related to the dosage in Vonoprazan patients [22]. In conclusion, in NSAIDs patients, the use of VPZ is recommended for the prevention of ulcer recurrence.

7.2 Ulcer recurrence prevention during low- dose aspirin therapy

Low dose aspirin is used to prevent thrombi formation in at-risk patients. Using this treatment, however, exposes the patient to possible recurrent ulcers. Thus, it is prescribed alongside PPIs to combat this side effect. One study on 574 patients

compared lansoprazole 15 mg and two Vonoprazan groups of 10 mg and 20 mg respectively.

The proportion of patients with endoscopically confirmed recurrent peptic ulcer during the 24-week treatment period (primary endpoint) was higher in the lansoprazole 15 mg group (2.8%; 6 of 213 patients) than in the vonoprazan 10 mg (0.5%; 1 of 197 patients) and vonoprazan 20 mg groups (1.5%; 3 of 196 patients). The differences in recurrence rate between the lansoprazole 15 mg group and the vonoprazan 10 mg and 20 mg groups were −2.3% and −1.3%, respectively. The non-inferiority of Vonoprazan to Lansoprazole 15 mg was verified ($p < 0.001$).

The differences in recurrence rates between vonoprazan 10 mg and lansoprazole 15 mg (−2.3%) and between vonoprazan 20 mg and lansoprazole 15 mg (−1.3%) were not statistically significant [23]. In conclusion, PPI or Vonoprazan are recommended for the prevention of low- dose aspirin therapy, including those with a history of ulcers or bleeding ulcers according to the Japanese guideline [3, 23].

8. Vonoprazan and gastroesophageal reflux disease (GERD)

As some patients with GERD are not controlled with their disease control under PPI, the vonoprazan therapy seems to be reasonable. In a retrospective study, GERD symptoms in the non-erosive group improved compared to baseline and remained better after 1 year of vonoprazan therapy, similar to the erosive group. Also, vonoprazan improved epigastric pain and postprandial distress symptoms in the non-erosive group and 1 year of vonoprazan therapy did not aggravate constipation or diarrhea [24]. A randomized controlled study on 73 patients with erosive esophagitis compared vonoprazan 20 mg (n = 37) or 10 mg (n = 36) for 4 weeks as the initial treatment followed by maintenance treatment with 10 mg for 8 weeks. The vonoprazan 10 mg group showed a similar therapeutic effect to the 20 mg group in mucosal healing at 4 weeks and in symptom relief throughout the study period [25]. A metaanalysis comprising six studies on this subject showed that vonoprazan is more effective than PPIs for patients with severe erosive esophagitis [26]. In the case of refractory patients, the behavioral disorders seem to be responsible for it in 20% of cases, so the high-resolution manometry, and 24-h multiluminal impedance pH-metry should be realized in such patients [27]. The level of pH should be higher than 5 for obtaining the clinical alleviation [28].

A cost-utility analysis proved that the Vonoprazan-first strategy increased quality-adjusted life years and appeared to be cost-effective for GERD patients compared with the esomeprazole- or rabeprazole-first strategies [29]. Intermittent use of Vonoprazan seems to be the most cost-efficient therapy in controlling GERD symptoms [30].

9. Conclusion

Vonoprazan has proven to be a viable and sometimes desired alternative to normal PPI treatment in case of ulcers or other circumstances that cause gastric acid imbalance. Its role in cost-efficiency analysis should be established in further studies.

Conflict of interest

The author declares no conflict of interest.

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