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REVIEW

Vonoprazan Fumarate for the Treatment of Gastric Ulcers: A Short Review on Emerging Data

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Abstract: Potassium-competitive acid blockers (P-CABs), such as vonoprazan, represent a novel and heterogeneous class of drugs that competitively block the potassium binding site of gastric H^+/K^+ ATPase, thus potentially overcoming the limitations of proton-pump inhibitors. Different studies evaluated the efficacy of vonoprazan versus proton-pump inhibitors (PPIs) for the treatment of acid-related disorders, and, therefore, P-CABs present the same indications of PPIs: gastroesophageal reflux disease, gastric and duodenal ulcer healing, management of upper gastrointestinal bleeding, non-steroidal anti-inflammatory drug (NSAID)-associated ulcers and *Helicobacter pylori* eradication therapy. The aim of this review was to evaluate the role of vonoprazan for the treatment of peptic ulcer disease (PUD) and the management of gastric ulcer occurring after endoscopic submucosal dissection (ESD). Indeed, vonoprazan (at the dose of both 10 and 20mg) showed similar results to PPIs in patients taking long-term NSAIDs, in the absence of severe adverse effects, and provided a more rapid and effective treatment of ulcers induced by ESD. However, studies in medical literature are heterogeneous, mainly performed with a retrospective design, and often carried out in Japan only. For these reasons, further prospective, randomized studies are warranted in order to help physicians, patients, and policymakers regarding the use of vonoprazan in clinical practice.

Keywords: gastric ulcer, P-CAB, adverse events, peptic disease, PPI, H2-receptor antagonists

Introduction

The therapeutic management of acid-related diseases and their complications have deeply changed with the development of proton-pump inhibitors (PPIs). Since their market release in the late 1980s, PPIs represented the mainstay for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), low-dose aspirin or non-steroidal anti-inflammatory drug-induced peptic ulcer and *Helicobacter pylori* (*H. pylori*) infection.[1–3] The first molecule introduced was omeprazole, followed by lansoprazole, pantoprazole, rabeprazole and esomeprazole.

PPIs are prodrugs that need acid to be activated and bind covalently to the gastric H^+/K^+ ATPase via disulfide bond. PPIs are metabolized and consequently inactivated by cytochrome P450 (CYP) enzymes, mainly CYP2C19 and CYP3A4.[4] Despite their proven efficacy, PPIs present several limitations, such as delay in action onset (3–5 days), low bioavailability, nocturnal acid breakthrough, drug interactions and intake at appropriate times relative to meals.[1] Moreover, they are affected by marked inter-individual variability of pharmacodynamics and clinical activity due to the existence of cytochrome polymorphisms. Four distinct phenotypes were indeed described: a)

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extensive metabolizers (EM); b) intermediate metabolizers; c) ultra-rapid metabolizers; d) poor metabolizers.[4] CYP2C19 is the main responsible for the metabolism of omeprazole, lansoprazole and pantoprazole, whereas, to note, rabeprazole undergoes a mainly non-enzymatic metabolism with renal elimination of its metabolites.[4] Furthermore, an increasing prevalence of antibiotic resistance associated with treatment regimens including PPIs for the eradication of *H. pylori* infection has been described.[1] Finally, recently, few safety concerns have been emphasized in different studies.[5]

The above considerations have stimulated the development of novel drugs in order to overcome PPI limitations and unmet clinical needs.[1,6-8] Potassium-competitive acid blockers (P-CABs) represent a novel and heterogeneous class of drugs that competitively block the potassium binding site of gastric H^+/K^+ ATPase. Following their absorption into the systemic circulation P-CABs are accumulated in the canalicular membrane of the parietal cells, where they are exposed to a highly acidic environment and promptly protonated. In contrast to PPIs, P-CABs are acid-stable and do not require enteric-coated formulations. Furthermore, P-CABs show a faster onset of acid inhibition and intragastric pH elevation than PPIs due to their ability of quickly achieving peak plasma levels after oral administration and consequently they block H+/K+ ATPase without requiring proton-pump activation.[1] Thanks to these features, P-CABs are able to reach a full antisecretory effect since the first dose assumption and to offer a more stable control of gastric pH than PPIs.

The first P-CAB used in clinical practice was revaprazan, available in South Korea and India since 2007.[4] Recently Takeda Pharmaceutical Company Limited (Japan) developed a novel and innovative P-CAB called vonoprazan, which is characterized by a potent, rapid and long-lasting effect, thanks to a reversible inhibition of gastric proton pump by a competitive block of the potassium binding site on the luminal surface of H^+/K^+ ATPase.[1] Vonoprazan is a weak base, with a higher value of alkaline pKa (>9) than previous P-CABs and PPIs and, when exposed to acid, undergoes an instant protonation and accumulate at high concentrations in the canaliculi of parietal cells, thus determining higher stability in an acidic environment than PPIs.[1,4] Vonoprazan is highly selective for binding to H^+/K^+ ATPase and is able to perform a powerful block of the gastric proton pump even in neutral conditions.[1] Furthermore, Vonoprazan dissociates from the proton pump slower than other P-CABs resulting in a longer duration of antisecretory effect.

Preclinical studies, both in vitro and in vivo, showed that the metabolism of vonoprazan is due to multiple hepatic metabolic enzymes.[1] In contrast to PPIs, vonoprazan metabolism has a limited influence by CYP polymorphisms and is metabolized to its inactive form mainly by CYP3A4.[4] Due to its rapid, strong and continuous gastric acid suppression, vonoprazan has been approved in Japan for the treatment of acid-related diseases.

There are different studies that evaluate the efficacy of vonoprazan versus PPIs. In fact, this drug has the same indications of PPIs: gastroesophageal reflux disease, gastric and duodenal ulcers healing, management of upper gastrointestinal bleeding, non-steroidal anti-inflammatory drugs (NSAIDs)-associated ulcers and *H. pylori* eradication therapy. The aim of this review is to evaluate the role of vonoprazan for the treatment of gastric ulcers through a deep revision of the literature.

Vonoprazan Therapy in Peptic Ulcer Disease

PUD is a chronic acid-related disease that usually occurs in the stomach or duodenum and is a common cause of gastrointestinal bleeding. The two main risk factors for PUD are *H. pylori* infection and the use of NSAIDs in patients at high risk. In the last decades of the twentieth century, the incidence of PUD began to decrease following two important developments: the synthesis of effective and potent acid suppressants such as PPIs and the discovery of *H. pylori*. However, despite the increasing recognition and eradication of *H. pylori*, it still affects up to 20% of adult population in Asia. As to the use of NSAIDs and/or aspirin, in the last decades, we witnessed an increase of their administration, particularly in the elderly population, due to the rising incidence of cardiovascular diseases and rheumatic disorders. To note, despite the use of NSAIDs and/or aspirin represents one of the major risk factors for upper gastrointestinal bleeding, discontinuing these therapies is often difficult (i.e. chronic pain, cardiovascular risk), and this requires the adoption of some measures to prevent a possible bleeding.

Due to its pharmacodynamic and pharmacokinetic advantages compared to PPIs, vonoprazan has been evaluated for the treatment of gastric ulcers. A randomized trial confirmed the non-inferiority of vonoprazan compared to lansoprazole in the treatment of gastric ulcer (93.5% and 93.8%, respectively), even if there was a possible bias due to the fact that drop-out subjects were put in the non-healed group. In this double-dummy

blind study, Miwa et al enrolled patients over the age of 20 years with at least one endoscopically confirmed gastric or duodenal ulcer and randomized them to receive lansoprazole (30 mg) or vonoprazan (20 mg) for 8 weeks.[9]

Other studies with vonoprazan (at the dose of both 10 and 20mg) showed similar results to PPIs in patients taking long-term NSAIDs, in the absence of severe adverse effects. Therefore, vonoprazan at the dose of 10mg has been approved for this indication.[10,11]

Management of Gastric Ulcer Occurring After Endoscopic Submucosal Dissection

The endoscopic treatment of pre-neoplastic or early-stage lesions of the digestive tract has evolved in the last 20 years. Indeed, nowadays we have a complex technique that allows us to remove the lesion en-bloc and reaches the muscular layer. This technique, called Endoscopic Submucosal Dissection (ESD), is based on the use of dedicated needles that, by cutting into the mucosa and submucosa, permit a radical "surgical" resection of lesions and a precise histological diagnosis.[12–15]

Nowadays, ESD is a very effective tool for endoscopic treatment of neoplasms located in the mucosa, but is complex and conceptually approaches surgical resection resulting in potential complications.[13] The main adverse events associated with ESD are represented by bleeding, perforation and pain. Bleeding is the most frequent event and occurs in a percentage of cases ranging from 5% to 8%. It is more frequent for gastric lesions than for the colon ones and the upper third of the stomach is more at risk of bleeding than the distal body and antrum. During the procedure, minor bleeds are very frequent and depend on the cut of submucosal vessels, while late bleeding (>72 hours) is usually rarer, smaller and tends to limit itself without the need for endoscopic therapies. Normally gastric ulcers induced by ESD heal within 8 weeks, but it is necessary to consider size, location, infection with *H. pylori*, and extent of gastric atrophy.[16,17]

PPIs are commonly prescribed in order to prevent bleeding and promote healing of gastric ulcers induced by ESD procedure. However, the most effective therapy for this condition remains controversial, because the data derived from literature are conflicting (Table 1). Ichida et al[18] performed a randomized controlled trial to evaluate the effects of vonoprazan plus rebamipide versus esomeprazole plus rebamipide on gastric ulcer healing induced by ESD. They demonstrated that there was no significant difference between the two drug combinations, but the delayed bleeding rate was lower in the vonoprazan plus rebamipide group, even though the statistical significance was not reached. In another prospective randomized study, Hamada et al[19] assessed the efficacy of vonoprazan versus lansoprazole in preventing delayed bleeding after gastric ESD. The bleeding rate in the vonoprazan group was significantly lower than the threshold rate, while this was not the same in the PPI group. Therefore, vonoprazan was found to be effective in preventing delayed bleeding even though the difference between the two drugs was small. In this Phase III

Table 1 Summary of Papers, Reviews and Meta-Analysis Included in This Paragraph

	Country	Study Design	Dose of Vonoprazan	Comparator (PPIs)	Number of Patients Included (Vonoprazan/PPIs)
Ichida et al 2019[18]	Japan	Prospective	20 mg	Esomeprazole	84 (44/40)
Hamada et al 2019[19]	Japan	Prospective	20 mg	Lansoprazole	139 (69/70)
Komori et al 2019[20]	Japan	Prospective	20 mg	Rabeprazole	40 (20/20)
Kakushima et al 2019[21]	Japan	Retrospective	20 mg	Rabeprazole/Lansoprazole/ Esomeprazole	130 (59/71)
Kim et al 2019[22]	Japan	Systematic review-meta analysis	20 mg	–	2005
Jaruvongvanich et al 2018[23]	Japan	Systematic review-meta analysis	10 mg/20 mg	Lansoprazole/Omeprazole	461 (215/246)
He et al 2019[24]	Japan	Systematic review-meta analysis	20 mg	Rabeprazole/Lansoprazole/ Esomeprazole	548
Kang et al 2019[25]	Japan	Systematic review-meta analysis	20 mg	Rabeprazole/Lansoprazole/ Esomeprazole	1265 (503/605)

study, a sub-analysis suggested that vonoprazan could reduce the incidence of bleeding in a particular class of patients, that is those with lesions larger than 2 cm or with an ulcer or scar located in the antrum. Komori et al[20] compared the efficacy of rabeprazole and P-CABs in the treatment of post-ESD gastric ulcers. At 4 weeks after the procedure, ulcer healing rate was significantly higher in the rabeprazole group, but this study presented some limitations including the small sample size, the short duration of protocol, and the fact that CYP2C19 polymorphisms were not investigated. Kakushima et al[21] compared the incidence of delayed bleeding after ESD between vonoprazan and various PPIs in patients who did not stop the assumption of antithrombotic drugs before the endoscopic procedure. Antithrombotic agents included either antiplatelet drugs (low-dose aspirin, cilostazol, etc.) and anticoagulants (warfarin or direct oral anticoagulant). This study was retrospective and evaluated a single-center experience, the sample size was small and PPIs were multiple, but also with these limitations the occurrence of delayed bleeding was not markedly different between the two groups and was higher among patients undergoing ESD during continuous antithrombotic treatment.

In medical literature, there are also systematic reviews and meta-analyses that evaluated the various articles currently present about the role of vonoprazan in the management of post-ESD gastric ulcers. Kim et al[22] published a network meta-analysis of all relevant controlled trials published from 2005 to October 2017 in order to compare the efficacy of various anti-ulcer medications after ESD. The primary endpoint was the efficacy of anti-ulcer drugs at 4 weeks and the secondary at 8 weeks post-ESD. Twenty-one RCTs were included with 2005 patients. At 4 weeks after ESD, the combination of PPI plus muco-protective agent was superior to PPI alone and vonoprazan, but vonoprazan resulted to be the most effective therapy at 8 weeks. The authors concluded that a first-line therapy with a combination of PPI plus muco-protective agent should be preferred, since it is probably more important to achieve a rapid healing of the iatrogenic ulcer due to the fact that the majority of bleeding episodes occur in the early phases after the procedure. However, this meta-analysis presented some limitations: the efficacy of vonoprazan was evaluated in 3 studies with small sample size and therefore the quality of evidence was rated as low or very low, various PPIs were used, there were no publications with languages other than English, and the superiority of vonoprazan at 8 weeks should be interpreted with caution.

Another systematic review and meta-analysis using Medline and Embase databases[23] evaluated comparative studies assessing the rate of complete healing and delayed bleeding of ulcers caused by ESD in patients who received vonoprazan versus PPIs. It considered only six retrospective and observational studies with a total amount of 461 patients and showed a significantly higher healing rate at 4–8 weeks after ESD in the vonoprazan group than in the PPI group, although the statistical significance was not reached. Furthermore, a more recent systematic review and meta-analysis,[24] that included seven published randomized clinical trials with a total amount of 548 patients, compared the use of vonoprazan and PPIs for the treatment of peptic ulcers resulting from ESD and considered the ulcer healing rate, the drug safety and the occurrence of unwanted events, such as perforation, delayed bleeding and hepatic injury between the two groups. The results showed no significant difference in the healing rate between the groups with a marginal superiority of PPIs. In terms of safety, this study showed fewer adverse events in the vonoprazan group but without statistical relevance. Finally, Kang et al[25] performed a systematic review and meta-analysis with the aim of comparing vonoprazan and PPIs in the treatment of ESD-induced ulcers and the prevention of delayed bleeding in randomized controlled trials and cohort studies. They did not observe significant differences between the two drugs in shrinkage rate (two studies, including 1 RCT and 1 cohort study) and in delayed bleeding (11 studies, including 6 RCTs and 5 cohort studies) at 4 weeks post-ESD. There was also no evidence of significant difference in ulcer size at week 0 (9 studies including 5 RCTs and 4 cohort studies) and at week 8 post-ESD (3 studies, including 2 RCTs and 1 cohort study), but, in contrast, ulcer size reduction at 4 weeks post-ESD was significantly higher in the vonoprazan group (4 RCTs). However, it has been shown a superiority of vonoprazan in ulcer healing rate in the early phase of the healing process. Indeed, vonoprazan offered a more rapid and effective treatment of artificial ulcers after ESD than PPIs. To note, this review included 1265 patients from 12 studies, but presented some limitations because the studies were heterogeneous, some evidences come from retrospective studies and all trials came from Japan.

In order to overtake the limitations of these reviews and in order to help physicians, patients, and policymakers regarding the use of vonoprazan in ESD-induced ulcers, Martin et al[26] have proposed a specific protocol for meta-analysis of randomized controlled trials and observational studies with the aim of assessing whether vonoprazan has better efficacy than PPIs for treating ESD-induced ulcers and preventing delayed bleeding at different lengths of treatment periods (2, 4 and 8 weeks). They included thirteen studies with follow-up at least longer

than 2 weeks, with measurements of shrinkage rate of post-ESD ulcers and with adequate number of people in ESD-induced scar stage and people with delayed bleeding. The researchers showed that vonoprazan was more effective than PPIs for treating *H. pylori*-positive patients with ESD-induced gastric ulcers during the first two weeks of treatment.[27]

Conclusions

Current data show that vonoprazan (at the dose of both 10 and 20mg) for the treatment of PUD is as effective as PPIs in patients taking long-term NSAIDs, in the absence of severe adverse effects. Moreover, vonoprazan offers a more rapid and effective treatment of artificial ulcers after ESD and is more effective than PPIs for treating *H. pylori*-positive patients with ESD-induced gastric ulcers during the first 2 weeks of treatment. However, available studies in medical literature are heterogeneous, mainly performed with a retrospective design, and often carried out in Japan only. For these reasons, further prospective, randomized studies are warranted in order to help physicians, patients, and policymakers regarding the use of vonoprazan in daily clinical practice.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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