Review paper

Vonoprazan in the management of erosive oesophagitis and peptic ulcer-induced medication: a systematic review

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Abstract

Introduction: Vonoprazan has been found to promote a better antisecretory effect addressing acid-related diseases' unmet needs.

Aim: To assess if vonoprazan effectively treats patients diagnosed with gastroesophageal reflux disease esophagitis or with peptic ulcers induced by chronic use of aspirin or non-steroidal anti-inflammatory drugs.

Material and methods: A literature search was conducted (April/2021) using Medline via PubMed, Cochrane library, Lilacs, Scielo, and Centre for Reviews and Dissemination electronic databases.

Results: We retrieved 55 titles. Of these, 13 met the eligibility criteria and were included in this review. Of these 13 articles, 4 were prospective cohort studies, 1 was a follow-up analysis of a preceding prospective study, 1 was a retrospective cohort study, and 6 were randomized clinical trials.

Conclusions: Our findings suggest that vonoprazan was effective and non-inferior to proton pump inhibitors in healing and maintaining healed reflux oesophagitis, leading to faster symptom relief. Vonoprazan may also be considered for preventing aspirin- or non-steroidal anti-inflammatory drug-related peptic ulcer recurrence.

Introduction

Gastroesophageal reflux disease (GERD) results when gastric contents reflux into the oesophagus; it is often accompanied by symptoms such as heartburn, acid regurgitation, and dysphagia. Although GERD itself is not fatal, its symptoms affect health-related quality of life and work productivity. Without effective treatment, serious complications such as oesophageal stricture, ulceration, or Barrett's oesophagus may develop [1].

Even at low doses, aspirin can cause gastrointestinal mucosal injury by inhibiting prostaglandin biosynthesis. However, low-dose aspirin (LDA) discontinuation can increase the risk of cardiovascular events for patients with a clear indication [2]. The same may occur with non-steroidal anti-inflammatory drugs (NSAIDs), commonly used to manage pain or inflammatory symptoms in chronic conditions. Although NSAIDs can cause gastrointestinal mucosal injury, their discontinuation is not always feasible because pain may recur and negatively impact the quality of life [3]. Therefore, it is clinically important to prevent mucosal injury while continuing LDA or NSAID therapy.

Gastric acid secretory inhibitors effectively treat GERD, peptic ulcer disease, and *Helicobacter pylori* infection and prevent LDA- or NSAID-induced peptic ulcers [4]. Proton pump inhibitors (PPIs), released in the late 1980s, dramatically improved gastric acid-related conditions [4]. Nowadays, potassium-competitive acid blockers (P-CABs) have emerged to promote a better antisecretory effect addressing these unmet needs associated with acid-related disease management, including but not limited to the treatment of advanced-grade erosive

oesophagitis, refractory GERD, and erosive oesophagitis maintenance treatment [5, 6].

The first P-CAB used in clinical practice was revaprazan, available in South Korea and India since 2007. Despite the early effect on acid suppression by revaprazan, there are no reports that revaprazan is more effective than PPIs for other gastric acid-related conditions [4]. In 2015, vonoprazan became available in Japan for the treatment of gastric ulcer, duodenal ulcer, and erosive oesophagitis, and to prevent LDA- or NSAID-induced ulcer recurrence [7, 8].

Aim

We conducted a systematic review to assess whether vonoprazan effectively treats patients diagnosed with GERD oesophagitis or with peptic ulcers induced by chronic use of aspirin or NSAIDs.

Material and methods

Study design

A systematic review of the current literature was conducted to answer the proposed objectives, using the PICO model (population; intervention; control; outcome). Thus, we searched for studies that evaluated whether vonoprazan effectively treats patients diagnosed with GERD oesophagitis or with peptic ulcers induced by chronic use of aspirin or NSAIDs.

Search strategy

A literature search was conducted through 22 April 2021, using Medline via PubMed, Cochrane Library, Lilacs, Scielo, and Centre for Reviews and Dissemination (CRD) electronic databases for the terms in Table I. Additionally, manual searches of bibliographic references and abstracts of selected publications complemented electronic searches.

Eligibility and inclusion and exclusion criteria

Studies to be considered eligible should meet the following inclusion criteria: meta-analyses, systematic reviews, and phase III or IV randomized controlled trials (RCTs) or observational studies; studies involving patients using vonoprazan to treat GERD esophagitis or those in chronic use of aspirin or NSAIDs; analysis with potassium pump inhibitors as a comparator or without comparator and efficacy endpoints trials. Furthermore, we excluded articles under at least one of the following conditions: narrative review, guidelines, consensus articles, editorials, case reports, or case series; studies involving patients with *Helicobacter pylori*; studies using animal models; articles published in languages other than English, Portuguese, and Spanish.

Table I. Search queries and retrieval numbers

Database	Search strategy
PubMed	(("Esophagitis"[Mesh] OR "Esophagitides" OR "Esophagitis, Peptic"[Mesh] OR "Esophagitides, Peptic" OR "Peptic Esophagitides" OR "Peptic Esophagitis" OR "Esophagitis, Reflux" OR "Esophagitides, Reflux" OR "Reflux Esophagitides" OR "Reflux Esophagitis" OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "NSAID" OR "Nonsteroidal Anti-Inflammatory Agent" OR "Agent, Nonsteroidal Anti-Inflammatory" OR "Anti-Inflammatory Agent, Nonsteroidal" OR "Nonsteroidal Anti Inflammatory Agent" OR "NSAIDs" OR "Antiinflammatory Agents, Non Steroidal" OR "Antiinflammatory Agents, Nonsteroidal" OR "Nonsteroidal Antiinflammatory Agents" OR "Non-Steroidal Anti-Inflammatory Agents" OR "Non Steroidal Anti Inflammatory Agents" OR "Nonsteroidal Anti-Inflammatory Agents" OR "Nonsteroidal Anti Inflammatory Agents" OR "Non-Steroidal Anti-Inflammatory Agent" OR "Agent, Non-Steroidal Anti-Inflammatory" OR "Anti-Inflammatory Agent, Non-Steroidal" OR "Non Steroidal Anti Inflammatory Agent" OR "Anti Inflammatory Agents, Nonsteroidal" OR "Analgesics, Anti-Inflammatory" OR "Anti-Inflammatory Analgesics" OR "Aspirin-Like Agents" OR "Aspirin Like Agents" OR "Aspirin-Like Agent" OR "Agent, Aspirin-Like" OR "Aspirin Like Agent") AND ("1-(5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl)-N-methylmethanamine" [Supplementary Concept] OR "Vonoprazan" OR "TAK 438" OR "TAK438" OR "TAK-438" OR "YH 1885" [Supplementary Concept] OR "YH-1885" OR "Revaprazan hydrochloride" OR "Revaprazan" OR "5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine" OR "tegoprazan" [Supplementary Concept] OR "tegoprazan" OR "1H-Benzimidazole-5-carboxamide, 7-(((4S)-5,7-difluoro-3,4-dihydro-2H-1-benzopyran-4-yl)oxy)-N,N,2-trimethyl-" OR "(S)-4-((5,7-difluorochroman-4-yl)oxy)-N,N,2-trimethyl-1H-benzo(d)imidazole-6-carboxamide" OR "7-(((4S)-5,7-Difluoro-3,4-dihydro-2H-chromen-4-yl)oxy)-N,N,2-trimethyl-1H-benzimidazole-5-carboxamide"))
Lilacs	("Vonoprazan")
Scielo	("Vonoprazan")
CRD	("Vonoprazan")
Cochrane	("Vonoprazan")

CDR – Centre for Reviews and Dissemination, LILACS – Literatura Latino-Americana e do Caribe em Ciencias da Saude.

Quality assessment

The risk of bias of the included studies was evaluated using the Cochrane tool for assessing the risk of bias, Risk of Bias 2 (RoB 2) tool, or Joanna Briggs Institute checklist for quasi-experimental studies [9, 10].

Data synthesis

Data extracted from included studies were synthesized and reported as tables and figures. Additionally, information was stratified according to the comparator arm (none or proton pump inhibitors (PPI)).

Results

Study selection

Studies were selected after removing duplicate records, and we retrieved 55 titles. After applying the eligibility criteria, 2 reviewers selected 26 studies for a full reading. Of these, 13 were chosen and included in this review (Figure 1).

Studies characteristics

Of the 13 articles included in this qualitative analysis, 4 were prospective cohort studies, 1 was a follow-up study of a preceding prospective study, 1 was a retrospective cohort study, and 7 were randomized clinical trials. The number of patients ranged from 16 to 732, totalling 3703 patients included in the selected studies. A list of the included studies and the description of their general characteristics according to the comparator type are presented in Table II.

Efficacy of initial therapy

In a prospective study, oesophageal mucosal breaks were successfully treated by vonoprazan 20 mg once daily for 4 weeks in 21 (87.5%) out of 24 patients with PPI-resistant reflux oesophagitis [2]. In 3 comparative studies, vonoprazan 20 mg demonstrated non-inferior efficacy versus lansoprazole 30 mg in terms of erosive esophagitis healing rate at 8 weeks in a population with erosive oesophagitis [11–13].

In patients with endoscopically confirmed GERD, heartburn was relieved sooner with vonoprazan 20 mg than with lansoprazole 30 mg ($p < 0.05$). Heartburn was relieved entirely in 31.3% and 12.5% of patients on day 1 with vonoprazan and lansoprazole, respectively. Significantly more patients achieved complete nocturnal heartburn relief with vonoprazan than with lansoprazole ($p < 0.01$) [14].

In a retrospective study, the efficacy of vonoprazan on PPI-resistant refractory reflux oesophagitis after oesophagectomy with gastric pull-up was evaluated. A 20 mg/day dose of vonoprazan significantly improved mucosal breaks in 81.3% of the treated patients compared to patients who continued PPI use (14.3%, $p < 0.001$). Additionally, vonoprazan aided mucosal healing in 68.8% of the patients compared to continued PPI use (7.1%, $p = 0.001$). Vonoprazan 20 mg could improve mucosal breaks in patients with refractory reflux esophagitis who had undergone esophagectomy with gastric tube reconstruction [3].

Efficacy of maintenance therapy

In 5 open-label prospective studies, vonoprazan 10 mg once daily showed effective 8-week [11], 24-week [6], 48-

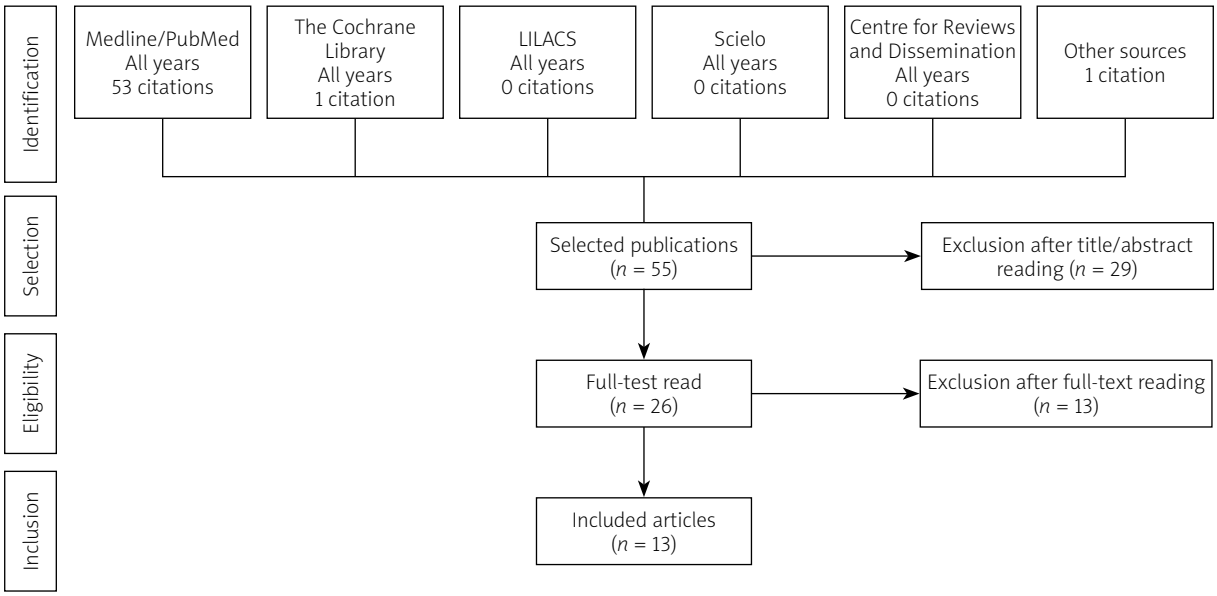

Figure 1. Study flow chart

Table II. Characteristics of selected studies and clinical profile of patients

Author, year [ref.]	Local	Population	Intervention	Comparator	Efficacy endpoints
Mizuno, 2020 [15]	Japan	50 patients aged ≥ 20 years, with RE refractory to PPIs who had no endoscopic evidence of erosive esophagitis after the administration of VPZ 20 mg OD/ 4 weeks	Vonoprazan 10 mg OD/ 48 weeks (maintenance)	–	• Endoscopic remission rate at 48 weeks • Proportion of patients with symptomatic relapse at 48 weeks
Mizuno, 2018 [6]	Japan	52 patients aged ≥ 20 years, with RE refractory to PPIs who had no endoscopic evidence of erosive esophagitis after the administration of VPZ 20 mg OD/ 4 weeks	Vonoprazan 10mg OD/ 24 weeks (maintenance)	–	• Maintenance of healed RE refractory to PPIs following 24 weeks • Proportion of patients with symptomatic non-relapse at 24 weeks
Umezawa, 2018 [17]	Japan	29 patients with mild RE receiving maintenance therapy with PPIs	Vonoprazan 20 mg OD/ 24 weeks (on-demand)	–	• Remission rate after 6 months • Overall satisfaction with the treatment
Tanabe, 2019 [16]	Japan	16 patients with RE refractory to PPIs	Vonoprazan 20 mg OD/ 4 weeks and vonoprazan 10 mg OD/8 weeks (maintenance)	–	• Endoscopic remission at 52 weeks
Hoshino, 2017 [2]	Japan	24 patients with PPI-resistant RE	Vonoprazan 20 mg OD/ 4 weeks and vonoprazan 10 mg OD/8 weeks (maintenance)	–	• Endoscopic healing in 4 and 12 weeks • Daily symptoms of RE (FSSG)
Ochiai, 2021 [3]	United States	30 patients with PPI-resistant RE	Vonoprazan 20 mg OD	Lansoprazole 30 mg OD Esomeprazole 40 mg OD Rabeprazole 20 mg OD	• Rates of improved mucosa and mucosal healing
Xiao, 2020 [11]	Asia	468 patients with endoscopically confirmed EE	Vonoprazan 20 mg OD up to 8 weeks	Lansoprazole 30 mg OD up to 8 weeks	• EE healing rate at 8 weeks • EE healing rate at 2 and 4 weeks • Subjective symptoms in patient diaries • HRQoL over 8 weeks Percentage of days without rescue medication • Safety endpoints
Ashida, 2018 [18]	Japan	607 patients ≥ 20 years, who presented with endoscopically-confirmed healed EE after vonoprazan 20mg OD/up to 8 weeks	Vonoprazan 20 mg OD/ 24 weeks (maintenance)	Lansoprazole 15 mg OD/24 weeks (maintenance)	• Rate of endoscopically-confirmed EE recurrence during a 24-wk maintenance period • EE recurrence rate at week 12 during maintenance treatment
Kawai, 2018 [19]	Japan	621 patients (439 in extension) with long-term LDA-associated peptic ulcers	Vonoprazan 10 mg OD or vonoprazan 20 mg OD/ 24 weeks (double blind) and ≤ 2 years (extension)	Lansoprazole 15 mg OD/24 weeks (double blind) and ≤ 2 years (extension)	• 24-week and 12-week peptic ulcer recurrence rate • 24-week GI bleeding rate • Cumulative incidences of peptic ulcer recurrence and GI bleeding

Table II. Cont.

Author, year [ref.]	Local	Population	Intervention	Comparator	Efficacy endpoints
Mizokami, 2018 [20]	Japan	642 patients receiving long-term NSAID therapy who are at risk of peptic ulcers recurrence	Vonoprazan 10 mg OD or vonoprazan 20 mg OD/ 24 weeks (double-blind) and 28–80 weeks (extension)	Lansoprazole 15 mg OD/24 weeks (double-blind) and 28–80 weeks (extension)	• Proportion of patients with recurrent peptic ulcer during 24 weeks of treatment • Proportions of patients with recurrent peptic ulcer up to 12 weeks • Proportion of patients with endoscopically proven bleeding in the stomach at weeks 12 and 24 • Time to an event of peptic ulcer
Oshima, 2019 [14]	Japan	32 patients ≥ 20 years with endoscopically confirmed EE and a recent history of at least weekly heartburn episodes	Vonoprazan 20 mg OD/ 14 days	Lansoprazole 30 mg OD/14 days	• First day of full day and night heartburn relief for at least 7 consecutive days • Total FSSG, reflux, and dyspepsia symptoms on days 7 and 14 • Pittsburgh Sleep Quality Index (PSQI) scores on days 14 and 0
Ashida, 2016 [13]	Japan	401 patients (305 in extension) with endoscopically confirmed EE	Vonoprazan 20 mg OD/ 8 weeks (comparison) and vonoprazan 10 mg or 20 mg OD/52 weeks (maintenance)	Lansoprazole 30 mg/ 8 weeks	• Proportion of healed EE patients up to week 8 • Proportion of patients with EE recurrence
Ashida, 2015 [12]	Japan	732 patients ≥ 20 years with endoscopically confirmed EE	Vonoprazan 5 mg, vonoprazan 10 mg, vonoprazan 20 mg or vonoprazan 40 mg OD/8weeks	Lansoprazole 30 mg OD/ 8 weeks	• Proportion of healed EE subjects as shown by endoscopy at week 4 • Proportion of healed EE subjects as demonstrated by endoscopy at weeks 2 and 8 • Subjective symptoms associated with EE

PPI – proton pump inhibitor, RE – reflux esophagitis, OD – once daily, FSSG – frequency scale for the symptoms of gastroesophageal reflux disease, EE – erosive esophagitis, LDA – low-dose aspirin.

week [15], and 52-week [13, 16] maintenance therapy of healed reflux oesophagitis or erosive oesophagitis refractory to PPIs [6, 11, 13, 15, 16]. On-demand therapy using 20-mg vonoprazan tablets is also an effective alternative maintenance therapy for mild reflux esophagitis [17].

The non-inferiority of vonoprazan 10 and 20 mg to lansoprazole 15 mg as maintenance therapy for patients with healed erosive oesophagitis was confirmed in a study that compared lansoprazole 15 mg, vonoprazan 10 mg, and vonoprazan 20 mg [18].

GERD symptoms

The median frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) score was significantly lower on days 1–7, 14, and 28 after the initiation of vonoprazan than before its administration in prospective studies with no comparator [2]. A comparative study showed total FSSG scores were significantly improved on days 7 and 14 by vonoprazan and on day 14 by lansoprazole [14]. At the end of the 24-week 10-mg-vonoprazan maintenance period, the symptomatic non-relapse rates for acid reflux-associated and dysmotility symptom FSSG scores were 86.5 and 80.8%, respectively [6]. During the 48-week 10-mg-vonoprazan maintenance therapy, the symptomatic non-relapse rates for acid reflux-related symptom score of FSSG and acid reflux score of the Gastrointestinal Symptom Rating Scale at 48 weeks were 70.0 and 72.0%, respec-

tively [15]. In another study, no significant difference was noted in the FSSG score between 8 and 52 weeks of 10-mg VPZ administration [16].

LDA- or NSAID-induced peptic ulcers

Vonoprazan (10 and 20 mg) was also as effective as lansoprazole (15 mg) in preventing LDA-induced peptic ulcer recurrence in a 24-week and long-term extension therapy study [19]. In the same way, non-inferiority of vonoprazan (10 and 20 mg) to prevent NSAID-related peptic ulcer recurrence was verified in patients receiving long-term NSAIDs in a 24-week study. Beyond that, it was effective and well-tolerated for longer than 1 year, with a safety profile similar to lansoprazole (15 mg) [20]. Both studies recommend a daily vonoprazan dose of 10 mg as the clinical dose.

Discussion

The results of this systematic review demonstrate non-inferiority of 8-week or 8-week treatment with vonoprazan versus PPIs in reflux oesophagitis or erosive oesophagitis healing. One study demonstrated higher vonoprazan (20 mg) effectiveness than lansoprazole (30 mg) treatment for severe erosive oesophagitis. In addition, 10-mg-vonoprazan therapy showed effectiveness in maintaining healed reflux oesophagitis for up to 52 weeks. Also, complete sustained heartburn relief was achieved sooner with vonoprazan than with lansoprazole during the first week of therapy. Therefore, our analysis may provide helpful information for clinicians, enabling them to offer other treatment choices to patients with GERD.

A systematic review with Bayesian network meta-analysis to estimate the comparative efficacy of treatments between PPI and vonoprazan was previously conducted by Miyazaki *et al.* [21]. This analysis showed that the GERD healing effect of vonoprazan is non-inferior to other PPIs, except for rabeprazole [21], but vonoprazan showed more effectiveness than most PPIs in the severe erosive oesophagitis patient group [21]. Another systematic review and meta-analysis made a direct comparison of the therapeutic effects and adverse events between vonoprazan 20 mg and PPIs. The researchers found that vonoprazan is non-inferior to PPIs as therapy for patients with GERD. Subgroup analysis for patients with severe oesophagitis at baseline showed significantly higher results for vonoprazan than for lansoprazole, with an RR of 1.14 (1.06–1.22). The safety outcomes for vonoprazan were similar to those for PPIs [22].

Gastroesophageal reflux disease adversely affects the quality of life of patients. Therefore, treatment with acid secretion suppressors can improve the quality of life related to gastrointestinal symptoms other than those involving the oesophagus [1, 4].

Furthermore, daily vonoprazan 10 mg can be considered the recommended clinical dose for preventing LDA- or NSAID-related peptic ulcer recurrence in at-risk patients. Vonoprazan has the potential to be a clinically useful alternative to PPIs, especially for patients with high-risk factors.

A major limitation of this study is the exclusion of all publications in languages other than English, Portuguese, or Spanish. In addition, conducting a meta-analysis would provide more robust results to determine the outcome of interest.

Conclusions

Our findings suggest that vonoprazan was effective and non-inferior to PPIs in healing reflux oesophagitis. It also can be considered for preventing LDA- or NSAID-related peptic ulcer recurrence in at-risk patients. Complete sustained heartburn relief was achieved sooner with vonoprazan than with PPIs during the first week of therapy. Also, vonoprazan showed better results than lansoprazole analysis for patients with severe oesophagitis.

Conflict of interest

DC has received fees as advisory board member for Takeda. JPPMF and GD has received fees as speaker for Takeda. JLSG and CYS are Takeda Pharmaceuticals Brazil full-time employees.

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