Original paper

Vonoprazan a novel potassium competitive acid blocker; another leap forward

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Abstract

Introduction: The eradication rate of *Helicobacter pylori* (*H. pylori*) has decreased due to antibiotics resistance and inadequate acid suppression. Vonoprazan is a novel potassium-competitive acid blocker (P-CAB), which has a rapid and sustained acid inhibitory effect and may be more effective than conventional proton pump inhibitors (PPIs) in *H. pylori* eradication.

Aim: to study the efficacy and safety of vonoprazan as a component of first-line *H. pylori* eradication treatment compared with conventional PPI-based therapy.

Material and methods: This randomised (one to one) non-blinded study was conducted on 400 consecutive proven *H. pylori* infected patients, of whom 200 received vonoprazan-based triple therapy, while 200 patients received PPI-based triple therapy for 14 days. The study outcomes were evaluated as eradication rate and adverse events in both patient groups.

Results: The eradication rate was 86% in the vonoprazan group and 74.5% in the PPI group. The vonoprazan eradication rate was significantly higher than that of PPIs ($p = 0.004$). There was no significant difference regarding adverse events between both patient groups.

Conclusions: Vonoprazan-based therapy was more effective than PPI-based therapy as a first-line *H. pylori* eradication treatment. Vonoprazan was generally safe and well tolerated.

Introduction

Helicobacter pylori infection affects about 50% of the human population, with a wide spectrum of complications like chronic gastritis, peptic ulcer, gastric mucosa associated lymphoid tissue (MALT) lymphoma, and even gastric cancer [1, 2].

The eradication of *H. pylori* is mandatory to reduce peptic ulcer recurrence and minimise the risk of gastric cancer, as well as its main role in treating MALT lymphoma [3, 4].

The most widely prescribed first-line treatment for *H. pylori* eradication has been triple therapy with proton pump inhibitors (PPIs), amoxicillin (AMX), and clarithromycin (CLR) [5]. The eradication rate with this triple therapy is significantly reduced [6]. There are several explanations for that: low medicine compliance, high intra-gastric acidity, high bacterial load, and strain variability, but the most important cause is antibiotic resistance [7–9].

The first-line eradication therapy failure rate is about 60–70% and is caused mainly by CLR resistance [10]. Otherwise, the main cause of second-line eradication therapy failure is metronidazole resistance [11]. There is a 20–40% resistance rate to levofloxacin [12].

To overcome antibiotic resistance, guidelines recommend eradication regimens that use more kinds of drugs (quadruple therapy), higher doses of drugs, and longer durations (10–14 days) [13]. The Maastricht V/Florence Consensus Report recommends bismuth-containing quadruple therapy or concomitant therapy in areas of high CLR resistance [13].

To exert the effect of AMX and CLR, maintenance of intragastric pH around 6 to 7 is mandatory [14]. There-

fore, development of potent gastric acid secretion-lowering agents is desired to improve the eradication rate. Vonoprazan is a prominent P-CAB, which strongly inhibits gastric acid secretion [15, 16].

Like PPIs, vonoprazan inhibits H^+, K^+-ATPase-mediated gastric acid secretion. However, unlike PPIs, inhibition is competitive, reversible, but longer due to the increased half-life of the drug, its action does not require acid activation and is not affected by ambient pH, and it accumulates in parietal cells under both secreting and resting conditions, so vonoprazan is more effective in elevating gastric pH than PPIs due to its ability to rapidly inhibit and maintain suppression of gastric acid secretion [17, 18]. This drug is also less affected by cytochrome P450 (CYP) 2C19 polymorphism because it is mainly metabolised by CYP3A4 [19].

In a randomised double blind phase III study, vonoprazan plus AMX and CLR showed an eradication rate of 92.6% as a first-line therapy for *H. pylori* eradication. Even in patients with CLR resistance, the eradication rate was 82.0%, which was significantly higher than traditional PPI-based therapy [15].

There are also many studies that revealed vonoprazan to be more efficient than PPIs in *H. pylori* eradication [20–22]. Vonoprazan can also improve the eradication of CLR and metronidazole-resistant *H. pylori* strains [23, 24]. Some studies even showed that dual therapy with vonoprazan and AMX can be as effective as triple therapy with vonoprazan, AMX, and CLR [25, 26].

Material and methods

Patient and study design

For this randomised (1/1), non-blinded study, 400 consecutive patients ≥ 18 years old were recruited from outpatient clinics in the National Liver Institute (NLI) and the Faculty of Medicine, Menoufia University. Cases were diagnosed with *H. pylori* infection between January 2022 and June 2022. *H. pylori* infection was confirmed in all patients using a 13C- urea breath test (UBT). The exclusion criteria were any history of *H. pylori* eradication therapy; pregnancy or lactation; history of allergy to any drug used; liver, renal, or heart dysfunction; history of drug or alcohol abuse; and history of malignancy.

At the start of the study, the demographics and characteristics of the patients were recorded. All patients were subjected to thorough physical examinations, vital signs assessments, laboratory tests (complete blood count, liver and kidney function tests), and electrocardiogram.

Patients were classified into 2 groups: the first group (200 patients) received vonoprazan-based therapy and the second group (200 patients) received conventional PPI-based therapy.

Eradication therapy

Once patients signed the consent form, they received eradication therapy for *H. pylori* for 14 days, the first group received vonoprazan 20 mg twice daily, and the second group received a high dose of conventional PPIs. Both groups received CLR 500 mg twice daily, AMX 1000 mg twice daily, and metronidazole 250 mg twice daily.

Study outcome

The primary outcome of our study was the rate of *H. pylori* eradication in both groups and patient characteristics that affected the eradication rate. Success or failure of eradication therapy was determined by 13C- UBT done at least 4 weeks after the end of treatment, with success defined as 13C- UBT ≤ 25%.

The secondary outcome was the adverse events of both regimens.

Statistical analysis

Data were fed to the computer and analysed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. The χ^2 test was applied to investigate the association between the categorical variables. For continuous data, they were tested for normality by the Kolmogorov-Smirnov test. Distributed data were expressed as range (minimum and maximum), mean, standard deviation, and median. The Mann-Whitney test was used to compare the 2 groups for non-normally distributed quantitative variables, and univariate logistic regression analysis was used to detect the effect of success rate of UBT. The significance of the obtained results was judged at the 5% level.

Results

Baseline characteristics of the patients

Our study included 400 patients, of whom 289 (72.3%) were males and 111 (27.8%) were females, with a mean of age of 38.7 ±11.6 years. Among all patients, 200 received vonoprazan-based therapy and 200 received PPI-based therapy. In the group receiving vonoprazan-based therapy, there were 143 (71.5%) males and 57 (28.5%) females, with mean of age 37.7 ±12.1 years, and in the group receiving PPI- based therapy, there were 146 (73%) males and 54 (27%) females, with a mean of age 36.6 ±11.2 years. In our study, there was no significant difference between both groups regarding age (p = 0.063), sex (p = 0.738), or smoking status (p = 0.08) (Table I).

Eradication rate

The eradication success rate was 86% (172 of 200 patients) in the vonoprazan-based therapy group and 74.5% (149 of 200 patients) in the PPI-based therapy group. So, our study revealed that the eradication rate was significantly higher in vonoprazan- than in PPI-based therapy ($p = 0.004$) (Table II).

Univariate regression analysis showed that age, sex, and smoking state had no effect on success of *H. pylori* eradication in the vonoprazan-based therapy group (Table III).

Adverse events

None of the documented adverse events were severe or led to discontinuation of treatment. In the vonoprazan group, there were 8 cases of diarrhoea (4%), 7 cases of nausea/vomiting (3.5%), 4 cases of constipation (2%), 7 cases of abdominal bloating (3.5%), 7 cases of abdominal pain (3.5%), 5 cases of taste disturbance (2.5%), 4 cases of stomatitis (2%), and 4 cases of skin rash (2%). None of the adverse events documented in the vonoprazan group were significantly more frequent than in the conventional PPI groups ($p > 0.05$) (Table II).

Discussion

According to our knowledge, this was the first study to assess the efficacy and safety of vonoprazan as a first-line therapy for *H. pylori* eradication in the Middle East.

Table I. Comparison between the 2 studied groups according to demographic data and smoking status

Parameter	Total ($n = 400$)	Group A ($n = 200$)	Group B ($n = 200$)	Test of Sig.	*P*-value
Age [years]:					
Mean ± SD	38.7 ±11.6	37.7 ±12.1	39.6 ±11.2	U = 17853.5	0.063
Median (min.–max.)	37 (18–66)	35.5 (18–66)	40.5 (18–65)		
Sex:					
Male	289 (72.3%)	143 (71.5%)	146 (73%)	$\chi^2 = 0.112$	0.738
Female	111 (27.8%)	57 (28.5%)	54 (27%)		
Smoking state:					
Non-smoker	189 (47.3%)	90 (45%)	99 (49.5%)	$\chi^2 = 5.040$	0.080
Smoker	171 (42.8%)	95 (47.5%)	76 (38%)		
Ex-smoker	40 (10%)	15 (7.5%)	25 (12.5%)		

SD – standard deviation, U – Mann-Whitney test, χ^2 – chi-square test, p – p-value for comparing between the studied groups. Group A – vonoprazan-based regimen, Group B – PPI-based regimen.

Table II. Comparison between the 2 studied groups according to outcome and adverse events

Parameter	Group A ($n = 200$)	Group B ($n = 200$)	χ^2	*P*-value
Outcome				
Urea breath test:				
Success rate	172 (86%)	149 (74.5%)	8.344*	0.004*
Failure rate	28 (14%)	51 (25.5%)		
Adverse events:				
Diarrhoea	8 (4%)	11 (5.5%)	0.497	0.481
Vomiting/nausea	7 (3.5%)	13 (6.5%)	1.895	0.169
Constipation	4 (2%)	7 (3.5%)	0.841	0.359
Abdominal bloating	7 (3.5%)	7 (3.5%)	0.000	1.000
Abdominal pain	7 (3.5%)	6 (3%)	0.080	0.778
Taste disturbance	5 (2.5%)	9 (4.5%)	1.184	0.276
Stomatitis	4 (2%)	7 (3.5%)	0.841	0.359
Rash	4 (2%)	10 (5%)	2.665	0.103

*χ^2 – Chi-square test, p – p-value for comparing between the studied groups. *Statistically significant at $p \leq 0.05$. Group A – vonoprazan-based regimen, Group B – PPI-based regimen.*

Table III. Comparison between success rate and failure rate according to demographic data in group A (vonoprazan-based regimen) (n = 200)

Parameter	Urea breath test		*P*-value	OR (95%CI)
	Success rate (n = 172)	Failure rate (n = 28)		
Age [years]:				
Mean ± SD	38.3 ±12.6	34.4 ±7.3	0.119	1.029 (0.993–1.067)
Median (min.–max.)	36.5 (18–66)	33.5 (22–50)		
Sex:				
Male	124 (72.1%)	19 (67.9%)	0.646	1.224 (0.518–2.892)
Female	48 (27.9%)	9 (32.1%)		1.000
Smoking state:				
Non-smoker	79 (45.9%)	11 (39.3%)		1.000
Smoker	81 (47.1%)	14 (50%)	0.617	0.806 (0.345–1.882)
Ex-smoker	12 (7%)	3 (10.7%)	0.417	0.557 (0.135–2.290)

*SD – standard deviation, OR – odds ratio, CI – confidence interval, LL – lower limit, UL – upper limit, p – p-value for odds ratio for comparing success rate and failure rate. *Statistically significant at p ≤ 0.05.*

Our study found that the eradication rate in patients using vonoprazan (86%) was significantly higher than in patients using conventional PPIs (74.5%) (p = 0.004).

According to the report card to grade *H. pylori* therapies, proposed by Graham *et al.* [27], the 74% eradication rate in PPI-based therapy constitutes an unacceptable grade (grade F). On the contrary, the 86% eradication rate in the vonoprazan-based therapy is an acceptable grade (grade C)

The high eradication rate of vonoprazan is consistent with a phase III, randomised, double-blind study, which compared vonoprazan-based therapy with lansoprazole-based therapy for *H. pylori* eradication in patients with gastroduodenal ulcers. The eradication rate in vonoprazan group (92.6%) was significantly higher than in the lansoprazole group (75.9%) (p < 0.0001) [15]. However, the eradication rate in our study was not as good as the one in this clinical trial. It is important to discuss the difference in the eradication rate. All of the patients in our study had an *H. pylori* infection, while the phase III trial included patients with a history of gastroduodenal ulcers. Clinically, *H. pylori* eradication therapy was administered to *H. pylori*-infected patients; thus, our results are more useful in clinical practice.

H. pylori eradication is affected by several factors including CYP2C19 polymorphisms, antibiotic susceptibility, age, smoking, and patient compliance [9, 24]. Insufficient gastric acid inhibition and antibiotic resistance are major factors causing *H. pylori* eradication failure [9, 24]. Gastric PH should be maintained near neutral throughout the day for *H. pylori* eradication [15].

In comparison with PPIs, vonoprazan requires no activation by acid [28], and it has higher bioactivity and greater stability in an acidic environment [21, 25]. It is rapidly absorbed and reaches maximum plasma concentration within 2 h after single administration [17, 29, 30]. The gastric PH increases above 4 as early as 4 h after single administration of vonoprazan [17], which enables it to elevate the PH of the stomach to near neutral, which in turn increases antibiotic activity and the metabolic activity of *H. pylori* making it more susceptible to antibiotics [23].

The eradication rate with vonoprazan was higher than that with PPIs in almost all studies [20, 21, 31–41], although Shinozaki *et al.* reported no significant differences between vonoprazan and esomeprazole [42].

Previous reports showed that eradication rates of vonoprazan-based therapy were between 83% and 96% when used as a first-line therapy and between 72% and 96% when used as a second-line therapy [43, 44].

Sakurai *et al.* reported that the eradication rate for vonoprazan, esomeprazole, rabeprazole, and lansoprazole were 87.9%, 71.6%, 62.9%, and 57.3%, respectively. So, the vonoprazan eradication rate was significantly higher than that of the PPIs (p < 0.01) [36], and Tsujimae *et al.* also reported that the first-line eradication rate was 86.3% in vonoprazan-based treatment and 79.9% in esomeprazole-based treatment [38].

A systematic review performed by Jung *et al.* with 10,644 patients in 10 studies revealed that the *H. pylori* eradication rate was 88.1% in patients who received vonoprazan and 72.8% in those who received PPIs [44].

A meta-analysis including 14 studies with 14,636 patients concluded that the eradication rate of vonoprazan-based therapy is much higher than that of PPI-based therapy when used as a first-line treatment. This

difference was significant for both intention-to-treat (85.1% for vonoprazan vs. 68.0% for PPI, $p < 0.00001$) and per-protocol analyses (89.0% for vonoprazan vs. 74.2% for PPI, $p < 0.00001$) [45].

A multicentre retrospective study done on 2715 patients showed that the eradication rate was 87.2% for vonoprazan-based therapy and 72.4% for conventional PPI-based therapy ($p < 0.01$) [20].

A recent study done on 19 patients with 2 failed therapies; they received vonoprazan (20 mg), AMX (750 mg), and rifabutin (150 mg) twice daily for 10 days, and the eradication rate was 100% [46].

Treatment of *H. pylori* is challenging due to increasing resistance to antibiotics, particularly CLR. The Maastricht V/Florence Consensus Report stated that PPI-CLR-containing triple therapy without prior susceptibility testing should be abandoned in regions where the CLR resistance rate is above 15% [13].

Okubo *et al.* reported that the eradication rate of vonoprazan was 91.6% in CLR-sensitive strains and 89.4% in CLR-resistant strains, and they concluded that vonoprazan was effective and well tolerated irrespective of CLR susceptibility [47]. Also, Tanabe *et al.* concluded that empirical triple therapy with vonoprazan is effective even in areas with high rates of CLR resistance [40].

The inhibitory effect of PPIs is fluctuating and is associated with the CYP2C19 genotype, which does not affect vonoprazan metabolism [48]. The frequency of CYP2C19 genotype of rapid extensive metabolizers is about 30% of Asians and 80% of Caucasians [49].

Sakurai *et al.* compared vonoprazan and PPIs in patients carrying the CYP2C19 rapid metabolizer genotype. The gastric PH 1 and 7 days after administration of vonoprazan was significantly higher than that after administration of esomeprazole or rabeprazole [50].

A recent study revealed that no significant differences were observed in the eradication rate of vonoprazan-based therapy among CYP3A4, CYP3A5, and CYP2C19 genotypes [51].

Reported adverse effects of vonoprazan include diarrhoea, nasopharyngitis, dysgeusia, flatulence [15], erythema multiforme [52], and high frequency of rash [37]. In our study, there were a few mild to moderate adverse events, which did not lead to discontinuation of treatment. There was no significant difference between vonoprazan and conventional PPI-based therapy regarding adverse events ($p > 0.05$). Hence, we conclude that vonoprazan-based therapy is safe and well-tolerated.

The incidence of adverse events was lower in the vonoprazan group than in the PPIs group in 2 randomized control trials and one propensity score-matched analysis [15, 21, 37]. However, this incidence was higher in the vonoprazan group than in the PPI group in 3 nonrandomised control trials [33, 34, 36].

Jung *et al.* reported that adverse event rates were 8.1% for vonoprazan-based treatment and 8.2% for PPI-based treatment. So, there was no significant difference between both groups [44].

In a study done on 1688 patients with *H. pylori* infection who received vonoprazan based therapy, the eradication rate was 90.8% and there was no severe adverse effect [22]. Dong *et al.* also reported in their meta-analysis that the safety of vonoprazan was equal or even superior to that of PPIs [45].

Suzuki *et al.* reported that there was no significant difference between vonoprazan and PPIs regarding adverse events except skin rash, which was significantly higher in vonoprazan therapy [37].

In our study, univariate regression analysis showed that the *H. pylori* eradication rate of vonoprazan-based therapy was not affected by age, sex, or smoking state.

Some studies reported that the *H. pylori* eradication rate in patients using PPI-based therapy was higher in males [53, 54]. However, there was no difference between genders in vonoprazan-based therapy [15, 36, 38].

Murakami *et al.* reported that advanced age had a mild but significant effect on the eradication rate of vonoprazan [15]. Kusunoki *et al.* concluded that the eradication rate was highly significant in patients using vonoprazan than in those using PPIs. However, this superiority of vonoprazan was remarkable in non-elderly patients and unclear in elderly patients [55].

Smoking can lead to *H. pylori* eradication failure because it stimulates acid secretion [5, 56], affects the metabolism of CYP P450 [57], and decreases gastric blood flow and mucous secretion [58]. Indeed, Suzuki *et al.* [59] reported that smoking increased the risk of *H. pylori* eradication failure. In our study, the eradication rate was not affected by smoking, so vonoprazan is effective even in smokers.

The reason why smoking did not affect the eradication rate was not clear. Strong acid suppression induced by vonoprazan might conceal the effect of smoking [60–62].

In a comparative study between vonoprazan, esomeprazole, rabeprazole, and lansoprazole, smoking did not affect the eradication rate in the vonoprazan group ($p = 0.34$), whereas it decreased the rates in the PPI groups ($p = 0.013$) [36].

Our study had certain limitations. First, it was not a double-blind trial. However, the UBT used to assess the primary outcome is objective, and the technicians were blinded to the treatment regimen and the purpose of the research. Second, we did not investigate antibiot-

ic sensitivity and CYP2C19 polymorphism, which have been reported to be major factors related to the success of *H. pylori* eradication therapy.

Conclusions

Vonoprazan-based treatment was more effective as a first-line *H. pylori* eradication therapy than conventional PPI-based treatment. In addition, vonoprazan was generally safe and well-tolerated with no significant difference regarding adverse events between vonoprazan and PPI-based treatment.

Ethics approval

The research was approved by the Ethical Committee of National Liver Institute, Menoufia University, Egypt number: NLI IRB 00003413 FWA0000227.

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None.

Conflict of interest

The authors declare no conflict of interest.

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