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ORIGINAL ARTICLE

Efficacy and safety of vonoprazan as a component of the first- and second-line eradication regimens for *Helicobacter pylori*: a real-life Egyptian study

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ABSTRACT

Background: Vonoprazan, a new potassium competitive acid blocker, offers a rapid onset of action and a predictable antisecretory profile that is independent of the CYP2C19 genotype or parietal cell activity. This profile may enhance *Helicobacter pylori* eradication therapy.
Aim: This research compared vonoprazan and proton-pump inhibitors (PPI) in Egypt's first- and second-line *H. pylori* eradication regimens for effectiveness, safety, and tolerability.
Methods: A prospective, controlled, multicenter, parallel-assignment, and open-label study was designed to verify the superiority of vonoprazan versus PPI in first-line therapy (with amoxicillin and clarithromycin) or second-line therapy (with levofloxacin, doxycycline, and nitazoxanide) for *H. pylori* eradication. Patients received either vonoprazan- or PPI-based regimens for 14 days followed by a 4-week follow-up period. The primary efficacy endpoint is the rate of first-line eradication, while the secondary endpoint is the rate of second-line eradication among individuals who did not respond to first-line treatment. Safety and tolerability of both first- and second-line treatments were also assessed.
Results: Of the 1184 patients allocated to the study, 701 naïve patients received first-line therapy (355 patients received a triple vonoprazan-based regimen; 346 patients received triple PPI-based regimen), and 483 experienced patients received the second-line therapy (243 patients received quadrable vonoprazan-based regimen and 240 patients received quadrable PPI-based regimen). The first-line eradication rate was 91% in vonoprazan triple therapy versus 74.6% in PPI triple therapy ($P < 0.001$). The second-line eradication rate was 89.7% in vonoprazan quadrable therapy versus 78.3% in PPI quadrable therapy ($P < 0.001$). Both first- and second-line therapies were well tolerated with no remarkable adverse events or safety outcomes.
Conclusion: In both naive and experienced patients, vonoprazan-based treatment was statistically and substantially superior to omeprazole-based therapy in eradicating *H. pylori*.
Relevance for Patients: This work offers a promising approach for the treatment of Egyptian patients with *H. pylori* infection.

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1. Introduction

Helicobacter pylori, a Gram-negative, microaerobic human pathogen, is linked to non-cardia stomach cancer, chronic active gastritis, peptic ulcer disease (PUD), atrophic gastritis, and mucosa-associated lymphoid tissue (MALT) lymphoma. *H. pylori* infects almost half of the adult population worldwide, though it is prevalent across geographies, races, ages, and socioeconomic groups [1,2].

Most of those infected with *H. pylori* will develop either gastric (70 – 90%) or duodenal (90%) ulcers [3]. However, some with *H. pylori* infection remain asymptomatic [4].

Non-cardiac stomach cancer is the third most frequent cause of cancer deaths worldwide, with *H. pylori* responsible for 74.7% of cases. *H. pylori* infection remains a critical issue, contributing to stomach cancer and ulcers, which together cause over a million deaths worldwide annually [1].

Screening and treatment are needed for active *H. pylori* infections. Individuals with ongoing or a history of PUD (unless previously treated), low-grade MALT lymphoma, endoscopic excision of early gastric cancer, or individuals under 60 years old with unexplained dyspepsia and no warning symptoms should be tested for *H. pylori* [5].

H. pylori diagnosis requires tests with >90% sensitivity and specificity. Managing numerous gastroduodenal disorders requires accurate *H. pylori* diagnosis. Histological, culture, and fast urease tests require endoscopy and biopsy, whereas serology, urea breath test, and stool antigen detection do not [1].

A global meta-analysis found the stool antigen test (SAT) to be 94% sensitive and 97% specific for *H. pylori* infection. This method detected *H. pylori* antigen in feces. Antibiotics, proton-pump inhibitors (PPI), N-acetylcysteine, diarrhea, and gastrointestinal (GI) bleeding can impact SAT accuracy [1].

Polyclonal antibodies and monoclonal antibodies are utilized in either enzyme immunoassay (EIA)- or immunochromatography-based SATs for *H. pylori* detection. The monoclonal SAT is a quick, painless, and accurate way to determine if you have a current *H. pylori* infection. The EIA test, which detects anti-*H. pylori* IgG antibodies, is the most common and effective serological test for *H. pylori* [1].

Serological tests are unaffected by ulcers, bleeding, stomach atrophy, PPIs, or antibiotics, unlike other invasive and non-invasive investigations. Due to their low cost, speed, and patient acceptability, serological tests have been routinely employed as a screening tool in epidemiological investigations. Even after effective eradication, antibody levels in the blood can remain elevated for extended durations, making the serological test an unreliable method of evaluation [6].

H. pylori is an infectious disease treated with 2 – 3 antibiotics and PPI for 3 – 14 days [4]. Increasing intragastric pH with a PPI and two antibiotics eliminates *H. pylori*; when the intragastric pH exceeds 5, *H. pylori* can grow and become more antibiotic-sensitive [7,8].

A rise in antibiotic-resistant genotypes of *H. pylori* has contributed to a decline in recent *H. pylori* eradication rates, despite the continued use of conventional PPIs to inhibit gastric acid secretion [9].

The fast evolution of antibiotic-resistant *H. pylori* strains has a significant impact on the efficacy of eradication treatment. Antibiotic resistance is an ever-changing process, and the incidence of *H. pylori* antibiotic resistance varies greatly between countries, and even in areas within the same country [10]. The most recent agreement for *H. pylori* care in Egypt suggested the same first- and second-line medications as the worldwide recommendations [11]; however, numerous studies recommend identifying *H. pylori* antibiotic resistance.

Metwally *et al*. [12] mentioned that in Egyptian patients, *H. pylori* demonstrated more than 90% resistance to metronidazole and amoxicillin (AMO); minor resistance to erythromycin, azithromycin, and clarithromycin (CLA); and low resistance to moxifloxacin and levofloxacin (≤20%). Dual resistance was high for AMO/CLA and AMO/metronidazole, indicating that quinolones are preferred over CLA or metronidazole for first-line *H. pylori* therapy in Egypt.

To enhance eradication efficiency, antibiotics have been changed, and PPI doses have been increased. The increased rate of eradication promotes the production of potassium competitive acid blockers (P-CABs), a chemical that decreases acid output [13].

Similar to PPIs, the new oral P-CAB vonoprazan inhibits gastric H^+-K^+-ATPase, the enzyme responsible for the final step of stomach acid production [14]. In contrast to PPIs, vonoprazan inhibits the enzyme in a K^+-competitive and reversible manner [15].

To effectively eradicate an *H. pylori* infection, nighttime stomach acid suppression must be maintained over an extended period. The optimal pH range when the organism is growing and sensitive to antibiotics (e.g., CLA and AMO) is 6 – 7 [16]. Acid suppression achieved by currently available PPIs is often insufficient, both in terms of magnitude and duration, to reach this level throughout the entire 24-h period. However, P-CABs are most effective when used in conjunction with one or more antimicrobial drugs, due to their unique pharmacological profile [17,18].

There is no correlation between CYP2C19 genotype and parietal cell activation, and P-CABs have a rapid onset of action and a predictable anti-secretory profile. In particular, this profile has the potential to simplify complex eradication regimens and pave the way for the development of highly effective dual therapy, both of which would lead to better *H. pylori* treatment management [18,19].

Furthermore, research has demonstrated that vonoprazan (pKa: 9.4) accumulates in parietal cells and that the pH of the surrounding environment has little impact on its acid-inhibitory effect [20,21]. Vonoprazan administered in multiple doses (10 – 40 mg/day) for 7 days in healthy volunteers maintained the dose-dependent, potent, and rapid acid inhibitory effects observed at 24 h compared to single doses (10 – 20 mg) [22,23]. Vonoprazan is likely to be as effective as PPIs in *H. pylori* treatment due to its stronger acid inhibition [24].

Here, this study aimed to assess the effectiveness, safety, and tolerability of vonoprazan in combination with PPI in Egyptian patients for the treatment of *H. pylori*.

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2. Methods

2.1. Study design

This was a prospective, controlled, multicenter, parallel-assignment, and open-label study involving patients selected from the gastroenterology and/or tropical medicine departments, as well as inpatient and outpatient clinics, from 12 university centers across Egypt (i.e., Faculty of Medicine of Alexandria University, Al-Azhar University, Ain Shams University, Cairo University, Assiut University, Mansoura University, Tanta University, Minia University, South Valley University, Zagazig University, Benha University; Faculty of Medicine and National Liver Institute of Menoufia University). The study was conducted from January 1, 2022, to June 30, 2022.

The inclusion criteria were patients (i) above 18 years of matched age and sex, and (ii) provided written informed consent before study participation. The exclusion criteria were patients (i) with known allergy to any of the treatment drugs; (ii) refused to sign an informed consent; (iii) had surgery that might affect gastric acid secretion (upper GI resection or vagotomy), Zollinger–Ellison syndrome, or other gastric acid hypersecretion disorders; (iv) had serious neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, GI, urological, endocrinological, or hematological disorders; (v) need surgery, history of drug (including alcohol) abuse, history of malignancy, and female subjects who are pregnant or lactating; (vi) pregnancy or planning for pregnancy during the study period; and (vii) on PPIs, P-CABs, and/or antibiotics within 1 month before inclusion in the study.

Patients who fulfilled the study inclusion criteria were allocated to one group of study as follows:

(i) Group-I: Naïve patients (patients who did not receive any prior *H. pylori* eradication regimens)
   - Arm 1: Patients received vonoprazan triple therapy: CLA 500 mg twice daily (bis in die [BID]) + AMO 1 g BID + vonoprazan 20 mg BID for 14 days
   - Arm 2: Patients received the classic triple therapy: CLA 500 mg BID + AMO 1 g BID + PPI "omeprazole 40 mg" BID for 14 days

(ii) Group-II: Non-responders (patients who did not respond to the previous first-line eradication regimen):
   - Arm 1: Patients received vonoprazan-based non-bismuth quadruple therapy: levofloxacin 500 mg once daily (OD) + vonoprazan 20 mg BID + nitazoxanide 500 mg BID + doxycycline 100 mg OD for 14 days
   - Arm 2: Patients received the classic non-bismuth quadruple therapy: Levofloxacin 500 mg OD + PPI "omeprazole 40 mg" BID + nitazoxanide 500 mg BID + doxycycline 100 mg OD) for 14 days.

2.2. Data collection

A total of 1200 patients were enrolled at the beginning of the study and were further divided into two equal-sized groups, each containing 600 subjects. The subjects were blindly allocated to vonoprazan and traditional PPI therapies. At the end of the study, two patients from the vonoprazan group did not complete the study, and 14 patients from the PPI group voluntarily stopped the drug regimen and did not complete the study.

The final sample size was 1184 patients, and they were divided accordingly in the study: 701 naïve patients received first-line therapy (355 patients received a triple vonoprazan-based regimen, and 346 patients received a triple PPI-based regimen), and 483 experienced patients received the second-line therapy (243 patients received quadrable vonoprazan-based regimen, and 240 patients received quadrable PPI-based regimen). After recruitment and allocation, all patients were subjected to the following:

(i) Full history and complete clinical examination: stool analysis, urine, complete blood count, *H. pylori* antigen (Ag) in stool (quantitative assay), and serum creatinine.

(ii) The presence of *H. pylori* was confirmed by the *H. pylori* SAT before study treatment administration and 4 weeks after the treatment regimen; antibiotics and acid-suppressive therapies were discontinued 2 weeks before doing the test.

During follow-ups, the patients were contacted by telephone after 1 week of starting the regimen to check compliance. The first follow-up visit was after completing 2 weeks of treatment to register any adverse events. The second follow-up visit was after completing 4 weeks of the treatment regimen to register the eradication results.

The primary purpose of the trial was to increase the rate of first-line *H. pylori* elimination. The second endpoint was the rate of H. pylori elimination in those who failed the first line of therapy.

The incidence of treatment-emergent adverse events was recorded. The principal investigator supervised the assessment of the safety of triple and quadrable therapy for *H. pylori* eradication in the local population.

2.3. Statistical analysis

The sample size was calculated using Power Analysis and Sample Size software (PASS 2020; ncss.com/software/pass; NCSS, LLC., USA). The minimal total hypothesized sample size of 800 eligible patients (400 per group) is required to compare the efficacy of vonoprazan and PPI in Egypt's first- and second-line *H. pylori* eradication regimens. This calculation assumes a 25% effect size (i.e., a minimally clinically important difference), a 95% confidence level, a 1:1 compliance ratio, and 80% power, using the Chi-square test [25,26]. The sample size was estimated based on the formula:

$$Sample\ size\ (n) = N \times \frac{[\frac{Z2 \times p \times (1-p)}{e2}]}{N-1+[\frac{Z2 \times p \times (1-p)}{e2}]} \quad (I)$$

Where N is the population size, Z is the critical value of the normal distribution at the required confidence level, p is the sample proportion, and e is the margin of error.

Data were fed to the computer and analyzed using IBM Statistical Package for the Social Sciences software version 20.0 (IBM Corp., USA). A Chi-square test was applied to compare

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different categories. The significance of the obtained results was judged at the 5% level.

3. Results

Table 1 presents the age of the participants; most participants (33.3%) aged 20 – 30 years, while the smallest percentage (0.3%) aged over 70 years. Moreover, female participants slightly outnumbered male participants (50.3% vs. 49.7%, respectively). There were also more naïve patients than experienced patients (58.5% vs. 41.5%, respectively).

Table 2 indicates that vonoprazan-based treatment outperformed omeprazole-based therapy in eradicating *H. pylori* in both naïve ($P < 0.001$) and experienced ($P = 0.001$) patients. However, vonoprazan-based treatment did not significantly vary between naïve and experienced groups ($p_0 = 0.504$).

Table 3 documents the adverse events experienced by patients. From the 598 vonoprazan-treated patients, five reported nausea/vomiting, ten with diarrhea, eight with constipation, two with bloating, and six with rashes, but none of them were severe.

Table 4 shows different regimens for previous Helicobacter pylori treatment. Among the 483 experienced patients, 119 (24.64%) of them received PPI, amoxicillin and clarithromycin, and 154 (31.88%) patients received PPI, amoxicillin and quinolones.

4. Discussion

Vonoprazan was just recently brought to the Egyptian market in early 2022, though it has been available in Japan and a few other nations since 2015. This is the first multicentric Egyptian study of vonoprazan triple therapy for *H. pylori*.

Standard triple treatment (STT) with PPIs, AMO, and CLA is unsuccessful in many countries due to *H. pylori* developing CLA resistance. Four-drug combinations, such as bismuth-containing quadruple therapy (BQT) or concurrent quadruple therapy, are first-line therapies for such diseases [27,28].

In previous studies, the eradication rates were 55 – 72% for STT within 7 days [25,29], 80 – 95% for BQT [30,31], and 86 – 91% for concomitant quadruple therapy (CQT) [32] as first-

Table 1. Distribution of the studied cases according to different parameters (n=1184)

Parameter	Number of patients (%)			Test of significance	*P*-value
	Total (n=1184) (%)	Group I (n=586) (%)	Group II (n=598) (%)		
Age (years)					
20 – 30	394 (33.3)	203 (34.6)	191 (31.9)	χ^2=7.934	0.160
31 – 40	353 (29.8)	179 (30.5)	174 (29.1)		
41 – 50	236 (19.9)	120 (20.5)	116 (19.4)		
51 – 60	149 (12.6)	63 (10.8)	86 (14.4)		
61 – 70	49 (4.1)	21 (3.6)	28 (4.7)		
>70	3 (0.3)	0 (0)	3 (0.5)		
Sex					
Male	589 (49.7)	300 (51.2)	289 (48.3)	χ^2=0.973	0.324
Female	595 (50.3)	286 (48.8)	309 (51.0)		
Weight (kg)					
Min-Max	69.0 – 121.0	69.0 – 121.0	69.0 – 121.0	t=0.672	0.502
Mean±SD	92.13±15.0	92.72±14.84	92.13±15.0		
Median (IQR)	95.0 (78 – 105)	96.0 (78 – 105)	95.0 (78 – 105)		
Height (cm)					
Min–Max	150.0 – 188.0	150.0 – 188.0	150.0 – 188.0	t=0.034	0.973
Mean±SD	170.06±10.67	170.0±10.59	170.1±10.67		
Median (IQR)	172.0 (161 – 180)	172.0 (161 – 179)	172.0 (161 – 180)		

χ^2 refers to the Chi-square test; t refers to Student's t-test; p refers to the p-value obtained from comparing groups I and II. Abbreviations: SD: Standard deviation; IQR: Interquartile range

Table 2. Comparison between omeprazole- and vonoprazan-based therapy in naïve and experienced patients

Patients	Number of patients (%)		*P*	p_0	
	Omeprazole (%)	Vonoprazan (%)		Omeprazole	Vonoprazan
Naïve (n=701)				0.293	0.504
Positive	88 (25.4)	32 (9.0)	<0.001*		
Negative	258 (74.6)	323 (91.0)			
Experienced (n=483)					
Positive	52 (21.7)	25 (10.3)	0.001*		
Negative	188 (78.3)	218 (89.7)			

"Positive" and "Negative" refer to the drug effect experienced by the patients; *P* denotes *P*-value from the Chi-square test comparing omeprazole- and vonoprazan-based therapy; p_0 denotes *P*-value from the Chi-square test comparing naïve and experienced patients; *denotes statistical significance at P<0.05

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Table 3. Adverse events of vonoprazan-based triple therapy versus conventional proton-pump inhibitor (PPI)-based triple therapy

Adverse effect	Number of patients (%)	
	Vonoprazan (*n*=598) (%)	Conventional PPI (*n*=586) (%)
Rash	6 (1.003)	7 (1.19)
Constipation	8 (1.33)	9 (1.5)
Diarrhea	10 (1.6)	11 (1.8)
Nausea and vomiting	5 (0.8)	3 (0.5)
Bloating	2 (0.3)	1 (0.17)

Table 4. Regimen for previous *Helicobacter pylori* treatment (*n*=483)

Regimen	Number of patients (%)
PPI+amoxicillin+clarithromycin	119 (24.64)
PPI+amoxicillin+quinolones	154 (31.88)
PPI+amoxicillin+metronidazole	117 (24.22)
PPI+amoxicillin+nitazoxanide+clarithromycin	93 (19.26)

Abbreviation: PPI: Proton-pump inhibitor

line *H. pylori* eradication treatments. The vonoprazan, AMO, and CLA triple treatment had eradication rates equivalent to the BQT and CQT and higher than the 7-day STT rate in this study.

We found that vonoprazan-based triple treatment had a higher eradication rate than PPI-based triple therapy as a first-line regimen in naïve patients (91% vs. 74.6%) and as rescue therapy in experienced patients (89.7% vs. 78.3%) in this study.

Consistent with previous findings, vonoprazan-based triple therapy achieved eradication rates exceeding 90%, while PPI-based triple therapy achieved rates of 80% [33]. The triple therapy that includes vonoprazan is preferable because its acid-inhibitory effect is more rapid, potent, and stable [34], and its pharmacokinetic features are not affected by CYP2C19 polymorphism [23].

Dual vonoprazan-AMO and CLA triple treatment eradication rates may be high because the strain infecting participants was not AMO resistant. Despite AMO resistance being lower than other antibiotics, it is often overlooked in *H. pylori* treatments. AMO resistance rates are 38% in Africa, 14% in the Eastern Mediterranean, 12% in Southeast Asia, 8% in the Americas, and 0 – 1% in Europe and the Western Pacific, though it varies significantly in other regions [35].

After 7 days of triple treatment, high-dose PPIs eliminated *H. pylori* infection more effectively compared to conventional doses (82% vs. 74%; 95% confidence interval [CI]: 1.01 – 1.17) in a previous meta-analysis [36]. Increased stomach pH may cause *H. pylori* to re-replicate and become antibiotic-sensitive [9]. If CLA resistance is >15%, many guidelines recommend avoiding PPI-CLA triple therapy [37]. Notably, 40% of patients in Egypt are resistant to CLA [12].

However, PPI-CLA triple therapy is frequently employed in the absence of CLA susceptibility testing, as empirical treatment is less time-consuming and less expensive than testing. Vonoprazan-CLA triple treatment eliminated CLA resistance more effectively than PPI-CLA triple therapy (82.0% vs. 40.0%; 95% CI: 3.63 – 12.86), demonstrating an acceptable eradication rate (i.e., >80%) [38].

When there is no CLA susceptibility test, vonoprazan-CLA triple therapy may be advised empirically. For 14 days, we compared vonoprazan-AMO-CLA treatment to PPI-based therapy for naïve patients and evaluated vonoprazan, nitazoxanide, levofloxacin, and doxycycline to a comparable PPI regimen for experienced patients. Our findings were similar to Mahrous *et al*., who did a similar study on Egyptian patients and compared the effects of vonoprazan, although with a smaller number of patients, included only one center, and used metronidazole instead of CLA in the naïve patients [39].

Our study included only adult participants and did not assess the effect of the drug in children with *H. pylori*. In addition, only three patients over 70 years old were included; hence, further studies are warranted to confirm the efficacy of vonoprazan in children and older adults, especially those with multiple medications and comorbidities.

The drug was well tolerated, with diarrhea being the most reported side effect. This may be linked to the use of CLA, which is known to stimulate GI motility. This finding contrasts with Furuta *et al*., who reported a higher incidence of diarrhea and other side effects with vonoprazan, potentially due to ethnic differences [40].

Nonetheless, this study had limitations, with the primary challenge being how to effectively communicate with the large number of patients and ensure their adherence and compliance to the treatment regimen.

5. Conclusion

In both naive and experienced patients, vonoprazan-based treatment was statistically substantially superior to omeprazole-based therapy in eradicating *H. pylori*. However, the effectiveness of vonoprazan-based treatment was not significantly different between naïve and experienced groups. Therefore, it appears to be a potentially safe and effective *H. pylori* treatment for our Egyptian patients, who tolerated it with few adverse effects.

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Conflict of Interest

There is a financial conflict of interest with the funder Inspire Pharmaceutical Company.

Ethics Approval and Consent to Participate

This study was approved by Alexandria University and was conducted in line with ethical principles. Moreover, the study protocol adheres to the ethical principles outlined in the

1975 Declaration of Helsinki. The trial was retrospectively registered on October 20, 2022; the trial registration serial number is 0305757, and the reference number is FWA NO: 00018699. Each participant's consent was acquired in advance. Patients provided written informed consent before participating in this research.

Consent for Publication

Patients who took part in this study agreed to publish their data.

Availability of Data

The materials supporting the study's results are included in the article. Additional information is accessible through the following link: https://drive.google.com/drive/folders/1m9wImunKzTJIV5H8zx1D3-_PYh1KsJ4L?usp=sharing

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