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Submission date: 28-Jul-2020 03:20PM (UTC+0800)
Submission ID: 1363159963
File name: 6._Vonoprazan_Review_Article-Final_AcxYAR_280720.docx (147.18K)
Word count: 6746
Character count: 38717

The Potential Benefits of Vonoprazan as *Helicobacter pylori* Infection Therapy

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Abstract

Helicobacter pylori infection is a severe global health problem and strongly associated with acid-related diseases and gastric malignancies. Eradicating *H. pylori* is strongly recommended for lowering peptic ulcer recurrence and preventing gastric cancer. The current approved *H. pylori* eradication regimen is combining proton pump inhibitor (PPI) with two antibiotics. Unfortunately, this regimen failed to meet expectations mostly due to antibiotics resistance and insufficiency gastric acid suppression. Vonoprazan, a novel drug from potassium-competitive acid blocker agent, showed promising results as a PPI replacement. Vonoprazan inhibits gastric acid secretion by acting as a reversible competitive inhibitor against potassium ion and forming disulfide bonds with cysteine molecule of H^+/K^+-ATPase. Vonoprazan has better pharmacological characteristics than PPI, such as no requirement of acid activation, stable in acid conditions, shorter duration to achieve optimum acid suppression, and lack of CYP2C19 polymorphism impact. Several comparative randomized controlled trials and meta-analysis studies revealed Vonoprazan superiority in eradicating *H. pylori* notably the resistant strains. The adverse effect caused by Vonoprazan is long-term acid suppression that may provoke elevated gastrin serum, hypochlorhydria, and malabsorption. All Vonoprazan studies were only still conducted in Japan, therefore further studies outside Japan is necessary for accepting globally.

Keywords: *Helicobacter pylori*, acid suppression agents, proton pump inhibitor, potassium-competitive acid blocker, Vonoprazan.

Introduction

Helicobacter pylori is a unique human-specific pathogen and can be found in the human stomach about 40-50% of the total human population. *H. pylori* infection is one of the global health problem whose prevalence is about 44.3%, range about 34.7% in developed countries and 50.8% in developing countries with global recurrence rate range in 4.3-4.6%.[1–3] An epidemiology meta-analysis study revealed that *H. pylori* infection is most prevalent in Africa (79.1%), followed by Latin America (63.4%) and Asia (54.7%).[4] Meanwhile in our country, Indonesia, the *H. pylori* infection prevalence is about 22.1%, suggesting *H. pylori* infects 1 of 4-5 our populations.[5] *H. pylori* infection is well correlated with incidences of gastritis, gastroesophageal reflux disease, gastroduodenal ulcers, gastric mucosal-associated lymphoid tissue (MALT) lymphoma, and gastric malignancies.[6–9] Eradication of *H. pylori* is critical due to its benefits such as reducing peptic ulcer recurrence, principal therapy of gastric MALT lymphoma, and minimizing risks of gastric cancer.[10–12]

H. pylori elimination therapy commonly uses PPI-based combination therapy for 7-14 days by combining PPI and minimum of 2 antibiotics. PPI takes a crucial role in *H. pylori* eradication by suppressing gastric acid secretion hence enhancing antibiotics efficacies.[13] However, the success rate of PPI-based eradication therapy declines as antibiotics resistance emergence and inadequate acid suppression.[13,14] Escalating PPI dosage does not increase successful eradication rate of PPI-based regimens.[15–17] Vonoprazan is a new potential gastric acid suppression agent through H^+/K^+-ATPase inhibition and classified into Potassium-Competitive Acid Blockers (P-CAB).[18,19] Vonoprazan has been advised by Japanese guidelines to replace PPI in first-line and second-line *H. pylori* eradication therapies since first introduced in 2015.[20] Several non-RCT, RCT, and meta-analysis established encouraging results using Vonoprazan-based therapies in

eradicating *H. pylori*. Vonoprazan is expected to be a new candidate in *H. pylori* eradication regimens.

Methods

We collected all relevant studies after searching comprehensively using predefined keywords through online databases of PubMed, Web of Science, EMBASE, and The Cochrane Library. We searched all relevant articles with keywords (("Vonoprazan" OR "VPZ" OR "TAK-438" OR "Potassium-Competitive Acid Inhibitor") AND ("*Helicobacter pylori*" OR "*H. pylori*")) for Vonoprazan-based eradication regimens and (("Proton Pump Inhibitor" OR "PPI" OR "Omeprazole" OR "Lansoprazole" OR "Esomeprazole" OR "Rabeprazole") AND ("*Helicobacter pylori*" OR "*H. pylori*")) for PPI-based eradication regimens. We included all articles about comparative retrospective, RCT, and meta-analysis studies of *H. pylori* eradication therapies in human populations using both regimens until April 2020. Our exclusion criteria are animal and Non-English studies.

Previous Treatment

A fact that unsatisfying acid-suppressing therapy outcomes before PPI invention expedited researches to innovate obtaining new therapeutic agents. Initial studies revealed PPI has better effectiveness compared to Histamine-2 receptor antagonist (H2RA)-based therapies.[21] Eradication of *H. pylori* combines PPI with minimum of two antibiotics and may add bismuth in each regimen. Table 1 reviews *H. pylori* eradication regimens approved by the Indonesian Society of Gastroenterology and American College of Gastroenterology.[22,23]

Table 1. *Helicobacter pylori* Eradication Therapy Regimens

Drug	Dose	Duration
First Line		
PPI*	2 x 1	
Amoxicillin	2 x 1000 mg	7 – 14 days
Clarithromycin	2 x 500 mg	
If Clarithromycin-resistant strains >20%		
PPI*	2 x 1	
Bismuth subsalicylate	2 x 2 tablets	7 -14 days
Metronidazole	3 x 500 mg	
Tetracycline	4 x 250 mg	
Second line when Clarithromycin-based Therapy Failed		
PPI*	2 x 1	
Bismuth subsalicylate	2 x 2 tablets	7 – 14 days
Metronidazole	3 x 500 mg	
PPI*	2 x 1	
Amoxicillin	2 x 1000 mg	7 – 14 days
Levofloxacin	2 x 500 mg	
Third line when second line regimens failed		
PPI*	2 x 1	
Amoxicillin	2 x 1000 mg	7 – 14 days
Levofloxacin	2 x 500 mg	
Rifabutin	2 x 500 mg	

*PPI agents used are Omeprazole 20 mg, Lansoprazole 30 mg, Esomeprazole 40 mg, Rabeprazole 20 mg, Pantoprazole 40 mg.

Unfortunately, PPI-based therapies unmeet clinicians' expectations in eradicating *H. pylori* as a raise in antibiotics resistance evidence. Failure of first-line eradication therapy is caused by the emergence of Clarithromycin-resistant *H. pylori* strain whose failure rate up to 60-70%.[24,25] Otherwise, Metronidazole-resistant *H. pylori* is the main cause second-line eradication therapy especially in South East Asia.[26] Resistance against Levofloxacin has been emerged in some countries with resistance rate about 20-40%.[27–29] As declared earlier, increasing PPI doses does not improve the eradication rate significantly. Consequently, Vonoprazan was introduced as PPI substitution candidate in all-lines *H. pylori* eradication regimens as referred to Japanese guidelines.[20]

Pharmacological Aspects

Vonoprazan is acid-stable regimens that can act as fast-released therapy. Vonoprazan has maximum plasma concentration (C_{max}) which rises from 10 to 60 ng/mL in only 1.5-2 hours.[30,31] Vonoprazan has area under curve (AUC) from time 0 to infinity in a dose range of 1.14-1.32 and significantly influenced by intestinal meal absorption.[30–32] Although there is no significant difference in holding time ratio pH>4 and time elapsed to reach C_{max}, Vonoprazan has more salutary C_{max}, AUC, and half-life compared to those of PPI. Vonoprazan is a base drug with pKa>9.0 as it is more concentrated in secretory canaliculi of the gastric parietal cells than in plasma.[32,33] Another possibility is Vonoprazan has higher positive charged points.[34] Vonoprazan's distribution depends on albumin and alpha-1 acid glycoprotein.[30]

Vonoprazan is an active drug that does not require acid activation like PPI. Vonoprazan is primarily metabolized in the liver through cytochrome P450 CYP3A4 but also metabolized

partially by CYP2B6, CYP2C19, CYP2D6, and SULT2A1.[35,36] Pharmacokinetics interaction between Vonoprazan and Clarithromycin is a mutual interaction because Clarithromycin is strong CYP3A4 inhibitor thus reduce Vonoprazan metabolism.[37] Otherwise, PPI is metabolized primarily through CYP2C19 whose polymorphism as extensive metabolizer that affects PPI efficacies and pro-drug activation process.[35,38] Research about acid suppression agents developed dramatically after H^+/K^+-ATPase crucial role invention at the last stage of gastric acid secretion. PPI is a prodrug activated by acid and forms disulfide bonds with cysteine component of H^+/K^+-ATPase.[33,39] PPI reaches maximum acid stability after 3-5 days consumption.[40,41]

Lack of PPI potency in forming a gastric base environment urged researchers to discover alternative acid-suppressing agents. Another mechanism that can be an alternative is reducing potassium ions concentration to limit H^+/K^+-ATPase efficacy. P-CAB agents, includes Vonoprazan, act as a reversible competitive inhibitor against potassium ions in binding with H^+/K^+-ATPase.[42,43] Vonoprazan is stable in acid gastric secretory canaliculi environment and binds non-covalently to H^+/K^+-ATPase.[44] Vonoprazan dissociates gradually and represses newly-presenting H^+/K^+-ATPase for a sustained period, consequently can increase gastric pH approaching 7 approximately in 4 hours.[45] Difference of pharmacokinetics and pharmacodynamics between PPI and Vonoprazan is compiled in Table 2.[41,43]

Table 2. Pharmacological Comparisons Between PPI and Vonoprazan

Parameter	First Generation PPI	Second Generation PPI	Vonoprazan
Acid activation	Yes		No
Active drug	No		Yes
Acid Stability	No		Yes

Main P450 metabolizer	CYP2C19		CYP3A4
Meal's influence	Yes		No
Mechanism of Action	Covalent bond to gastric proton pump		Potassium ion competitive reversible inhibitor to gastric proton pump
Day required for reaching maximal acid suppression	3-5		1
pH>4 holding time (%)	OMZ 30.4	ESO 43.1	10 mg 38.4-43.1
	LPZ 39.1	RPZ 42.8	20 mg 62.7-63.3
Time Needed to Reach Maximum Plasma Concentration (h)	OMZ 1-4	ESO 1-3.5	10 mg 1.75
	LPZ 1.2-2.1	RPZ 1.14	20 mg 1.50
Half-life (h)	OMZ 0.5-1.2	ESO 1.3-1.6	10 mg 6.95 ± 1.03
	LPZ 0.9-2.1	RPZ 0.6-1.4	20 mg 6.85 ± 0.80
C_{max} (μmol/l)	OMZ 0.23-23.2	ESO 2.1-2.4	10 mg 9.7 ± 2.1 μg/l
	LPZ 1.62-3.25	RPZ 1.14	20 mg 25.0 ± 5.6 μg/l
AUC (μmol.h/l)	OMZ 0.58-3.47	ESO 4.2	10 mg 60.1 ± 9.0 μg.h/l
	LPZ 4.60-13.5	RPZ 2.22	20 mg 160.3 ± 38.6 μg.h/l

AUC: Area Under Curve, C_{max}: Maximum Plasma Concentration, OMZ: Omeprazole 20 mg; LPZ: Lansoprazole 30 mg; ESO: Esomeprazole 40 mg; RPZ: Rabeprazole 20 mg.

Vonoprazan and Gastroesophageal Reflux Disease

GERD is one of the diseases we often face in our daily practices with heartburn symptoms and quality of life disruption. Standard therapy of GERD is PPI yet the outcome is still unsatisfying. The previous study told that 30% of erosive esophagitis patients still complain about heartburn when sleeping during PPI therapy.[46,47] Another surprising study recorded that about 50% of GERD patients received PPI therapy did not meet their expectation and 20% of them did "shopping doctor" to seek additional medications.[48]

Vonoprazan has the potential to substitute PPI in GERD management. Switching PPI to Vonoprazan in erosive esophagitis can relieve symptoms quickly and significantly. A meta-analysis study proved the non-inferiority of Vonoprazan against PPI in GERD management and subgroup analysis noted that Vonoprazan significantly has better efficacy in healing erosive esophagitis.[49] Vonoprazan is also more effective healing erosive esophagitis in CYP2C19 EM patients than PPI with healing rate 90.0% and 79.3% respectively.[50]

Vonoprazan and Peptic Ulcers

Gastric and duodenal ulcer is one of the main chronic gastrointestinal problems. The gastroduodenal ulcer can be caused by *H. pylori* infection, long-term NSAIDs consumption, and idiopathic. Current standard therapy for healing peptic and duodenal ulcers is PPI. Vonoprazan is non-inferior against Lansoprazole in healing peptic ulcer whose recurrence rates are 3.3% and 5.5% respectively confirmed by endoscopy examination.[51] An RCT study confirmed Vonoprazan non-inferiority with peptic ulcer healing rate 93.5% compared to Lansoprazole 93.8%, unfortunately the study cannot confirm healing rate of duodenal ulcers due to dropped out patients and not healed ulcers.[52] Vonoprazan also has comparable efficacy with Lansoprazole in reducing

peptic ulcer recurrence incidence in patients consuming low dose Aspirin.[53] Meta-analysis study showed that patients whose peptic ulcer related to endoscopic gastric submucosal resection receiving Vonoprazan have statistically significant higher healing rate compared to those received PPI (pooled OR 2.27, 95% CI 1.38-3.73, I^2=0%, p=0.001).[54]

Vonoprazan and *H. pylori* Eradication

H. pylori eradication is essential for preventing and intervening long-term complications. There are numerous determinants influencing eradication rate during *H. pylori* eradication therapy: antibiotic resistance, acid suppression adequacy, virulence factors (*cagA*, *vacA*, *dupA*), and environments.[55–58] Previous *H. pylori* eradication therapy uses PPI-based regimens still unmet needs, somehow doubling PPI dose has low evidence and weak recommendation for eradication therapy.[17] Additionally, polymorphism CYP2C19 EM evidence diminishes PPI ability in suppressing gastric acid.

Vonoprazan has a strong candidacy replacing PPI in *H. pylori* eradication regimens. Vonoprazan has pharmacological advantages such as the absence of acid activation, stable in an acid environment, and more prolonged half-life.[55] Vonoprazan has been advised to replace PPI in Japanese guidelines of *H. pylori* eradication. Standardized first-line *H. pylori* eradication therapy is PPI, Clarithromycin, and Amoxicillin. Both RCT and non-RCT studies revealed Vonoprazan-based eradication regimens have higher eradication rate than PPI-based regimens (Table 3). Our previous meta-analysis includes 5 Clarithromycin-sensitive *H. pylori* RCT studies revealed no statistically significant difference of successful and failure eradication rate when we compare first-generation PPI-based and Vonoprazan based regimens (pooled RR 1.01, 95% CI 0.98-1.04, I^2=61%, p=0.04 and pooled RR 0.84, 95% CI 0.57-1.25, I^2=0%, p=0.39), still we found significant

differences of successful and eradication rates not only between second-generation PPI-based and Vonoprazan-based regimens (pooled RR 1.25, 95% CI 1.15-1.37, I^2=82%, p<0.00001 and pooled RR 0.31, 95% CI 0.23-0.42, I^2=50%, p<0.00001), but also combination of all PPI generation-based and Vonoprazan-based regimens (pooled RR 1.11, 95% CI 1.07-1.16, I^2=98%, p<0.00001 and pooled RR 0.43, 95% CI 0.34-0.55, I^2=81%, p<0.00001).[15] Several studies about Clarithromycin-resistant *H. pylori* showed a better eradication rate with Vonoprazan-based regimens (Table 4). A meta-analysis study concluded that Vonoprazan-based regimens have superiority in eradicating Clarithromycin-resistant *H. pylori* (pooled eradication rates 82% and 40%, pooled OR 6.83, 95% CI 3.63-12.86, I^2=0%, p<0.0001).[59]

Table 3. Review of Comparative Studies First-line *H. pylori* Eradication Therapy

Study	VPZ-based regimen		PPI-based regimen	
	Regimen	Eradication rate	Regimen	Eradication rate
RCT				
Murakami *et al*., 2016[60]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	90.9%	LPZ: 30 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	75.1%
Takimoto *et al*., 2017[61]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	33.3%	LPZ: 30 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	11.1%

Maruyama *et al*., 2017[62]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	95.8%	LPZ: 30 mg bid or RPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	69.6%
Sue *et al*., 2017[63]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	87.3%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	76.5%
Ozaki *et al*., 2018[64]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	90.9%	RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	72.8%
Non-RCT				
Suzuki *et al*., 2016[65]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	89.0%	LPZ: 30 mg bid or RPZ: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	74.2%

Shinozaki *et al*., 2016[66]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	82.9%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	73.9%
Shichijo *et al*., 2016[67]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	87.2%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	72.4%
Noda *et al*., 2016[68]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 400 mg bid	89.7%	OMZ: 20 mg bid, LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	73.9%
Matsumoto *et al*., 2016[69]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	89.6%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid	71.9%

			CLR: 200 or 400 mg bid	
Yamada *et al*., 2016[70]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	85.7%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	73.2%
Tsujimae *et al*., 2016[71]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	84.6%	ESO: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	79.1%
Kajihara *et al*., 2016[72]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 400 mg bid	94.6%	RPZ: 10 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	86.7%
Sakurai *et al*., 2017[73]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	87.9%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	66.9%
Sue *et al*., 2017[74]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	84.9%	OMZ: 20 mg bid, LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid	78.8%

			AMX: 750 mg bid CLR: 200 or 400 mg bid	
Nishizawa *et al*., 2017[75]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	62.3%	LPZ: 30 mg bid or RPZ: 10 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	47.1%
Tanabe *et al*., 2018[76]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	91.5%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	79.4%

AMX: Amoxicillin, CLR: Clarithromycin, ESO: Esomperazole, LPZ: Lansoprazole, OMZ: Omeprazole, RPZ: Rabeprazole, VPZ: Vonoprazan.

Table 4. Review of Comparative Studies First-line Clarithromycin-resistant *H. pylori* Eradication Therapy

Study	VPZ-based regimen		PPI-based regimen	
	Regimen	Eradication rate	Regimen	Eradication rate
RCT				

Murakami *et al*., 2016[60]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	82.0%	LPZ: 30 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	40.0%
Non-RCT				
Noda *et al*., 2016[68]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 400 mg bid	87.5%	OMZ: 20 mg bid, LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	53.8%
Matsumoto *et al*., 2016[69]	VPZ: 20 mg bid AMX: 750 mg bid CLR: 200 mg bid	76.1%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid CLR: 200 or 400 mg bid	40.2%

AMX: Amoxicillin, CLR: Clarithromycin, ESO: Esomeprazole, LPZ: Lansoprazole, OMZ: Omeprazole, RPZ: Rabeprazole, VPZ: Vonoprazan.

Second-line eradication therapy is used after the failure of first-line therapy, which consists of PPI, Amoxicillin, and Metronidazole. We did not find any RCT studies comparing the outcome of Vonoprazan-based and PPI-based second-line *H. pylori* eradication therapy (Table 5). Shinozaki *et al*. conducted meta-analysis study for all non-RCT studies and concluded that Vonoprazan-based second-line eradication regimens are statistically significant in eradicating *H. pylori* (pooled OR 1.51, 95% CI 1.27-1.81, I^2=0%, p<0.00001).[77]

Table 5. Review of Comparative Studies Second-line *H. pylori* Eradication Therapy

Study	VPZ-based regimen		PPI-based regimen	
	Regimen	Eradication rate	Regimen	Eradication rate
Yamada *et al*., 2016[70]	VPZ: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	89.6%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	89.9%
Tsujimae *et al*., 2016[71]	VPZ: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	89.1%	ESO: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	83.3%
Sakurai *et al*., 2017[73]	VPZ: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	96.1%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid	89.7%

			AMX: 750 mg bid MNZ: 250 mg bid	
Sue *et al*., 2017[74]	VPZ: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	80.5%	LPZ: 30 mg bid, RPZ: 10 mg bid or ESO: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	81.5%
Nishizawa *et al*., 2017[78]	VPZ: 20 mg bid AMX: 750 mg bid MNZ: 250 mg bid	71.8%	LPZ: 30 mg bid or RPZ: 10 mg bid AMX: 750 mg bid MNZ: 250 mg bid	73.7%

AMX: Amoxicillin, CLR: Clarithromycin, ESO: Esomperazole, LPZ: Lansoprazole, MNZ: Metronidazole, RPZ: Rabeprazole, VPZ: Vonoprazan.

Third-line *H. pylori* eradication regimen combines PPI or Vonoprazan, Amoxicillin, and Sitafloxacin. A study revealed that the third-line Vonoprazan-based regimen has higher *H. pylori* eradication rate than the PPI-based regimen (75.8% vs 53.3%).[79] Another study also revealed Vonoprazan-based regimen has better eradication rate in Sitafloxacin-resistant *H. pylori* than Esomeprazole-based regimens (91.7% vs 71.2%).[80] Study about third-line *H. pylori* eradication therapy is limited since it is not covered in Japanese health insurance coverage.[81]

The main limitation in this review is all studies were conducted in Japan hence make researchers and clinicians wonder about the efficacy of Vonoprazan outside Japan. Japanese people tend to have higher pH >4 holding time ratio than the UK population.[31,32] Besides, every

region has different antibiotic resistance mapping, for example, Japan has high Clarithromycin resistance rate (>30%) but low Metronidazole resistance rate (<5%).[82] The contradictory study conducted in Indonesia revealed that *H. pylori* in this country has low Clarithromycin resistance (9.1%) but high Metronidazole and Levofloxacin resistances with rates of 46.7% and 31.2% respectively.[29]

High incidence of *H. pylori* with poly-antimicrobial resistances drives the researcher to discover alternative *H. pylori* eradication therapy. Previously, we performed research to discover alternative therapy using Metronidazole-resistant and Levofloxacin-resistant *H. pylori* strains in Indonesia, Bangladesh, and Bhutan, through *in vitro* studies discovered that Furazolidones, Rifaximin, Rifabutin, Garenoxacin, and Sitafloxacin are effective in eradicating *H. pylori*.[29,83] Another alternative therapy is using anti-*Helicobacter pylori* herbal medicine such as Indian plant *Bombax ceiba*, or even a propolis *Trigona sp*. ethanol extract can inhibit the growth of Metronidazole-resistant and Levofloxacin-resistant *H. pylori* in *in vitro* study.[84,85]

Safety and Adverse Events

Since early P-CAB developed, the most recognized complication is hepatotoxicity though no serious adverse effects observed.[39,41] Unlike the previous P-CAB group which is a derivative of an imidazole-pyridine compound, Vonoprazan is a pyridine-derivative compound so that the hepatotoxicity risk becomes lower.[35,86] Nevertheless, some previous studies did not encounter any significant difference transaminases increment between patients receiving Vonoprazan and PPI.[30]

The effect of acid inhibition of Vonoprazan is better than PPI, as a consequence, the increment of gastrin serum in patients receiving Vonoprazan therapy is higher than in patients receiving PPI therapy.[16,50] Hypergastrinemia can trigger gastric enterochromaffin cell hyperplasia

and develop the risk of gastric endocrine tumors.[87,88] Hypochlorhydria precipitated by acid inhibition can alter the gut microbiome, increase prone to develop antibiotic-associated diarrhea caused by *Clostridium difficile* and spontaneous bacterial peritonitis.[89,90] Excessive acid suppression can also cause malabsorption resulting in the onset of iron deficiency anemia, megaloblastic anemia, hypomagnesia, and hypocalcemia.[43,91] Additional side effects that can emerge are interstitial nephritis, pneumonia, dementia, chronic kidney disease and ischemic heart disease.[92–94]

Conclusion

Vonoprazan can be future medication replacing PPI in gastroduodenal diseases mainly *Helicobacter pylori* eradication therapy. Vonoprazan has both better pharmacological and clinical superiorities than PPI. However, further Vonoprazan studies are required to confirm its efficacies, particularly clinical study outside Japan, therefore Vonoprazan can be accepted globally.

Acknowledgments

Riset Kolaborasi Mitra Luar Negeri tahun 2020 Grant from Universitas Airlangga (441/UN3.14/PT/2020).

Author Contributions

All authors have equal contributions in searching references, extracting data, drafting and approving the final manuscript.

Conflict of Interests

Authors have no conflict of interests to declare.

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