PharmaNote®

Vol. 37, Issue 12 September 2022 Established 1985

Using the PAK to Fight Back: Combating Helicobacter Pylori Infections with Novel Therapy

Nathalie Roumi, PharmD Candidate

Helicobacter pylori (H. pylori) is a gram-negative bacterium that can infect the stomach by adhering and colonizing the gastric epithelium. H. pylori can be transmitted person-to-person or through contaminated water supplies like rivers, streams, pools, and uncooked vegetables.[1] The prevalence of H. pylori infections is generally lower in developed countries like the United States compared to other parts of the world. However, in the United States higher rates of infection are associated with lower socioeconomic status and racial/ethnic groups including African Americans, Hispanics, Native Americans, and Alaska natives.[1]

H. pylori exclusively attaches and colonizes the gastric epithelium and releases cytotoxic enzymes that include urease, phospholipase, antioxidants, and proteolytic enzymes.[2] H. pylori survives in the stomach's acidic environment by activating its own cytoplasmic urease which converts urea into carbon dioxide and ammonia. The bacteria can thrive and colonize in the stomach through the neutralization of the gastric acid by ammonia preventing acidification of the bacterial inner membrane.[3] The risk factors are peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, gastric cancer, dyspepsia, gastroesophageal reflux disease (GERD), non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin use, iron deficiency anemia, and idiopathic thrombocytopenic purpura.[3]

One of two types of diagnostic tests is used to confirm H. pylori infection: non-invasive testing or endoscopic testing. Non-invasive testing includes urea breath testing, stool antigen assay, and serology, while endoscopic testing includes biopsy urease testing, histology, and bacterial culture.[4] Confirmation of eradication with a urea breath test, stool antigen assay, or endoscopic testing is necessary for all H. pylori patients due to high resistance rates and evaluation if further treatment is needed. Proton pump inhibitors (PPIs) are the cornerstone of treating gastric acid-related diseases such as H. pylori by irreversible binding to and directly inhibiting the H+/K+-ATPase in the parietal cells. According to the American College of Gastroenterology[4] the standard first-line treatment of H. pylori is split into five subcategories as described in **Table 1**.

Vonoprazan, a reversible potassium-competitive acid blocker, has been an established treatment in Japan since 2014. Vonoprazan-based treatment regimens with amoxicillin and clarithromycin have recently been approved for the treatment of H. pylori in the United States as of May 2022.[5] The purpose of this drug review is to explore the impact of vonoprazan in Voquezna© dual therapy, with amoxicillin, and Voquezna© triple therapy, with amoxicillin and clarithromycin, as well as explore its pharmacokinetic and pharmacodynamic parameters, clinical studies reviewing efficacy and antimicrobial resistance, and its clinical implications.

Pharmacology

Mechanism of Action

Vonoprazan is the first approved potassium-competitive acid blocker that suppresses acid secretion through the competitive inhibition of potassium on the H+/K+-ATPase at the surface of the gastric parietal cell.[6] Acid suppression is important to increase the stability and activity of antibiotics.

Amoxicillin is a penicillin antimicrobial that inhibits bacterial cell wall synthesis by binding to the penicillin-binding proteins that polymerize and modify peptidoglycan component of the bacterial cell wall.[6] Amoxicillin is a broad-spectrum antibiotic that covers gram-positive cocci, except Methicillin-resistant Staphylococcus aureus (MRSA), and gram-negative bacilli, except pseudomonas, as well anaerobes.

Clarithromycin is a macrolide antimicrobial that can be bacteriostatic or bactericidal depending on the concentration of the organism. Clarithromycin binds to the 50S subunit of the 70S ribosome which blocks bacterial protein synthesis.[6] Double antibacterial coverage has been increasingly important for the eradication of H. pylori due to increase in antimicrobial resistance.

Pharmacokinetics

With a rapid onset of 2 to 3 hours and time to maximum concentration of 2.5 hours after a single dose gastric pH, vonoprazan has a plasma-protein binding of 85% to 88%.[6] Vonoprazan undergoes hepatic cytochrome P450, sulfotransferase and glucuronosyl-transferase metabolism. It has a 7.1 hour half-life for a single dose and 6.8 hours at steady state. 67% of vonoprazan is excreted in the urine with 8% of unchanged

IN THIS ISSUE

Table 1 | First Line Therapies for *H. pylori* Infection[4]

Treatment Regimen	Medication	Dosing Frequency	Duration
Bismuth Quadruple	PPI[a]	Twice daily	10-14 days
	Bismuth subcitrate OR Bismuth subsalicylate	Four times daily	
	Tetracycline	Four times daily	
	Metronidazole	Three to four times daily (dependent of strength)	
Clarithromycin Triple	PPI[a]	Twice daily	14 days
	Clarithromycin	Twice daily	
	Amoxicillin OR Metronidazole	Twice to three times daily (dependent on medication)	
Clarithromycin-based Concomitant	PPI[a]	Twice daily	10 days
	Clarithromycin		
	Amoxicillin		
	Metronidazole OR Tinidazole		
Clarithromycin-based Sequential	**Step 1**: PPI[a] + Amoxicillin	Twice daily	5 days
	Step 2: PPI[a] + Clarithromycin + Metronidazole OR Tinidazole		
Clarithromycin-based Hybrid	**Step 1**: PPI[a] + Amoxicillin	Twice daily	7 days
	Step 2: PPI[a] + Amoxicillin + Clarithromycin + Metronidazole OR Tinidazole		

[a]Proton pump inhibitors standard dose: Lansoprazole 30 mg daily, omeprazole 20 mg daily, pantoprazole 40 mg daily, rabeprazole 20 mg daily, or esomeprazole 20 mg daily

drug; and 31% is excreted in the feces with 1.4% of unchanged drug.[6]

Amoxicillin also has a rapid onset, and it readily diffuses into body tissue and fluids, except for brain and spinal fluid. Amoxicillin is 20% protein bound and is approximately 60% excreted in the urine unchanged which can be delated by concurrent administration of probenecid. Amoxicillin has a half-life of 61 minutes and can be impacted by renal function.[6]

Clarithromycin has high intracellular concentration with a 42% to 70% plasma-protein binding. Clarithromycin is hepatically metabolized by CYP3A4 enzymes to its active metabolite, 14-OH Clarithromycin. Clarithromycin has a half-life of 5-7 hours and 14 -OH Clarithromycin has a longer half-life of 7-9 hours. Clarithromycin is excreted in the urine with 20-40% as unchanged drug and 10-15% as 14-OH Clarithromycin, and it is excreted in the feces mostly as the active metabolite.[6] Refer to **Table 2** for pharmacokinetic summary of vonoprazan, amoxicillin, and clarithromycin.

Clinical Trials

Voquezna Dual© and Triple PAK© were FDA approved for the treatment of H. pylori based on the efficacy and safety results from a phase III, randomized, open-label controlled trial.[5] Vonoprazan dual and triple therapy was also approved in Japan and widely used for H. pylori treatment. Researchers *Suzuki et al.* conducted a prospective, randomized clinical trial to compare the efficacy of vonoprazan dual therapy versus vonoprazan triple therapy.[7] Both studies were multicenter studies and a C-urea breath test (C-UBT) was used to assess treatment success. Refer to **Table 3** for the summary of primary outcomes from both studies.

Study 1 NCT04167670[5]

The efficacy and safety of vonoprazan dual and triple therapy was evaluated in a multicenter, randomized, controlled, phase 3 trial, and open-label vonoprazan dual therapy, double-blind vonoprazan triple therapy or lansoprazole triple therapy (lansoprazole 30mg, amoxicillin 1 gram, clarithromycin 500mg twice daily). A total of 1046 patients were randomized to 1:1:1 ratio; 262 patients assigned to vonoprazan triple therapy, 265 to vonoprazan dual therapy, and 255 to lansoprazole triple therapy (219, 218, 212 included in the per protocol analysis respectively).[5] Eligibility included age over 18 years old, treatment naïve, with a H. pylori infection confirmed positive C-UBT and had at least one of the following conditions: dyspepsia, a new diagnosis of nonbleeding peptic ulcer, history of peptic ulcer, or requirement for long-term NSAID use at a stable dose. The exclusion criteria included patients with gastric cancer, gastric or duodenal ulcer with current or recent bleeding, or GI bleeding within 4 weeks.[5]

The primary outcome was assessing the noninferiority in eradication rates in patients without Clarithromycin and Amoxicillin resistant strains. The eradication rate was set to be assessed by the C-UBT at week 6, four weeks after the last given dose. However, due to the COVID-19 pandemic, these results were obtained around 3 to 5 weeks after the last given dose.[5] The secondary outcome was assessing the superiority in eradication rates in clarithromycin resistant infections and in all patients. Vonoprazan dual therapy consisted of vonoprazan 20mg twice daily and amoxicillin 1g three times daily; with vonoprazan triple therapy adding clarithromycin 500mg twice daily. Both therapies were compared to lansoprazole 30mg twice daily with amoxicillin 1g three times daily and clarithromycin 500mg twice daily with a treatment duration of 14 days.[5]

Some limitations to this study include the study population limited to treatment naïve patients and vonoprazan dual therapy was open therapy due to its different dosing schedule. Moreover, this was a multicenter study in the United States and Europe, but sites had different number of patients contributing and were not evenly distributed geographically which limits generalizability.[5]

Vonoprazan triple therapy eradicated H. pylori in 84.7% (222 of 262) of patients and vonoprazan dual therapy eradicated H. pylori in 78.5% (208 of 265) of patients compared to 78.8% (201 of 255) for lansoprazole triple therapy (CI, -0.8 – 12.6; P<0.001; CI, -7.4 – 6.8; P=0.007, respectively). In the per protocol primary population, H. pylori was eradicated in 90.4% (198 of 219) of vonoprazan triple therapy patients, 81.2% (177 of 218) of vonoprazan dual therapy, compared to 82.1% (174 of 212) of lansoprazole triple therapy patients (CI, 1.9 – 15.0; P<0.001; CI, -

8.3 – 6.5; P=0.16, respectively).[5] This data shows that vonoprazan triple and dual therapies met the primary endpoint of non-inferiority compared to lansoprazole triple therapy in the full analysis, which was also maintained in the per protocol population.

In clarithromycin-resistant strains full analysis set, vonoprazan triple therapy eradicated H. pylori in 65.8% (48 of 73) of patients and vonoprazan dual therapy eradicated H. pylori 69.6% (39 of 56) of patients compared with 31.9% (23 of 72) of patients on lansoprazole triple therapy (CI, 20.6 – 53.4; P<0.001; CI 20.5 – 52.6; P<0.001, respectively). For per protocol set, eradication rates were 67.2% (39 of 58) and 79.5% (35 of 44) compared to 29.0% (18 of 62) (CI 20.6 – 53.4; P<0.001; CI 32.3 - 65.0; P<0.001, respectively).[5]

A full set analysis set of superiority in all patients showed the eradication rate with vonoprazan triple therapy was 80.6% (273 of 338) of patients and vonoprazan dual therapy was 77.2% (250 of 324) of patients compared with 68.5% (226 of 330) of patients on lansoprazole triple therapy (CI, 5.7 – 18.8; P<0.001; CI 1.9 – 15.4; P=0.013, respectively). For per protocol set, eradication rates were 85.7% (240 of 280) and 81.1% (215 of 265) compared to 70.0% (194 of 277) (CI 20.6 – 53.4; P<0.001; CI 3.9-18.2; P=0.003, respectively).[5]

Based on the primary outcome results presented, vonoprazan based triple and dual therapies were noninferior to lansoprazole triple therapy for the treatment of H. pylori strains not resistant to clarithromycin and amoxicillin. In the secondary analyses with clarithromycin resistant strains and all patients as shown in **Figure 1**, vonoprazan triple and dual therapies were superior to lansoprazole triple therapy.

Suzuki et al. 2020 Trial[7]

The efficacy of vonoprazan-based dual versus triple therapy was evaluated in a prospective, multicenter, open label, randomized clinical trial performed in Japan. The inclusion criteria included patients aged 20-79 years old and had a confirmed H. pylori infection confirmed by culture testing.[7] Patients with history of receiving H. pylori eradication therapy, allergy to any of the study drugs, history of gastric surgery, use of PPIs, antibiotics or steroids that could not have been discontinued during this study, pregnancy or breastfeeding, or lack of informed consent were excluded. The two therapies evaluated are vonoprazan dual therapy (vonoprazan 20mg and amoxicillin 750mg twice daily for 7 days) and vonoprazan triple therapy (vonoprazan 20mg, amoxicillin 750mg, and clarithromycin 200mg twice daily for 7 days).[7] The 335 eligible patients were randomly allocated to vonoprazan dual or triple therapy in a 1:1 ratio.[7] Out of 168 patients enrolled in vonoprazan dual therapy group, 5 were lost to follow-up, discontinued due to adverse event, or non-compliant; and out of 167 vonoprazan triple therapy group, 3 patients were excluded due to same reasoning.[7] The primary outcome of this study is H. pylori eradication rate which was evaluated using the C-UBT with success defined as <2.5% at least 4 weeks after treatment completion.[7] The secondary outcomes included the frequency and severity of adverse events and the comparison of eradication rates according to antimicrobial susceptibility. Some limitations of this study include being an open label study only done in Japan which minimizes generalizability.

Table 2 | Select Vonoprazan Pharmacokinetics[6]

Absorption	
T_{max}[a]	2.5 hours
Distribution	
V_{ss}[b]	1050 L
Protein Binding	85—88%
Metabolism	
CYP Enzymes	3A4/5, 2B6, 2C19, 2C9, 2D6
Elimination	
$T_{1/2}$[c]	7.1 hours
Fecal	31%
Urine	67%

[a]Time to maximum concentration; [b]Steady state volume of distribution; [c]Half-life

In the intended to treat (ITT) analysis, the H. pylori eradication rate was 84.5% (142/168); CI 78.2% to 89.6%) in the VA-dual group and 89.2% (149/167; CI 83.5% to 93.5%) in the VAC-triple group (p value for difference = 0.203; p value for non-inferiority = 0.073).[7] In the per protocol (PP) analysis, the H. pylori eradication rate was 87.1% (142/163; CI 81.0% to 91.8%) and 90.2% (148/164; CI 84.6% to 94.3%) in the vonoprazan dual and the vonoprazan triple therapy groups, respectively (p value for difference = 0.372; p value for non-inferiority = 0.024).[7]

The resistance rate of H. pylori to clarithromycin was 24.5% (82/335). The eradication rate in the vonoprazan triple therapy group was significantly higher than the vonoprazan dual therapy group in the clarithromycin susceptible strain (85.5% vs 95.1%, p = 0.011).[7] However, the eradication rate of vonoprazan triple therapy group was significantly lower than the vonoprazan dual therapy group in clarithromycin resistant strain (76.2% vs 92.3%, p = 0.267).[7] For amoxicillin therapy, MIC values were categorized into three groups: less than or equal to 0.015 (93.15%, 312/335), 0.03 (5.7%, 19/335), or 0.06 (1.25%, 4/335) ug/mL.[7] A summary of result is shown in **Figure 2**. Overall, all the results showed no statistical significance except for vonoprazan triple therapy group having a significantly lower eradication rate in the 0.06 MIC group than the less than or equal to 0.015 MIC group (25% vs 92.7%, p<0.001).[7]

Adverse events were reported using a questionnaire form

Table 3 | Primary Outcomes[5,7]

Trial	Outcome	Treatment Arms	Result (95% CI)	P-Value
Study 1 NCT04167670[5]	Eradication rate of infection	Vonoprazan Dual[a]	84.7% (-0.8 to 12.6)	<0.001
		Vonoprazan Triple[b]	78.5% (-7.4 to 6.8)	0.007
		Lansoprazole Triple[c]	78.8%	——
Suzuki et al.[7]	Eradication rate of infection	Vonoprazan Dual[d]	84.5% (78.2 to 89.6)	——
		Vonoprazan Triple[e]	89.2% (83.5 to 93.5)	

[a]Contains vonoprazan 20mg twice daily and amoxicillin 1 gram three times daily for 14 days; [b]Contains vonoprazan 20mg, amoxicillin 1 gram, and clarithromycin 500mg, each given twice daily for 14 days; [c]Contains lansoprazole 30mg, amoxicillin 1 gram, clarithromycin 500mg twice daily for 14 days; [d]Contains vonoprazan 20mg and amoxicillin 750mg twice daily for 7 days; [e]Contains vonoprazan 20mg, amoxicillin 750mg, and clarithromycin 200mg twice daily for 7 days.

assessing the severity using 1 to 4 grading system based on the Common Terminology Criteria for Adverse Events (CTCAE). The total adverse event rates were similar between vonoprazan dual and vonoprazan triple therapy groups similar to study 1. 91.4% of adverse events were mild (CTCAE grade 1) and 8.6% were moderate (CTCAE grade 2).[7]

Based on the results, the 7-day vonoprazan and low dose amoxicillin dual therapy provided acceptable H.pylori eradication rates and a similar effect to vonoprazan-based triple therapy in regions with high clarithromycin resistance. This is a good future alternative in the United States to be explored in order to minimize the antimicrobial resistance incidence.

Dosage and Administration

Voquezna© dual PAK consists of vonoprazan 20mg twice daily and amoxicillin 1,000mg three times daily. Meanwhile, Voquezna© triple PAK consists of vonoprazan 20mg, amoxicillin 1,000mg, and clarithromycin 500mg, each given twice daily 12 hours apart.[5] Both combinations can be given with or without food. The duration of therapy is 14 days. Missed dose should be administered as soon as possible within 4 hours of scheduled dose. If 4 hours have passed, the missed dose should be skipped, and regular dosing schedule should be resumed.[6]

Precautions

Hypersensitivity reactions like anaphylaxis can occur with component of vonoprazan dual and triple pak as well as severe cutaneous adverse reactions (SCAR).[6] Diarrhea occurring with vonoprazan should be evaluated for Clostridioides difficile-associated diarrhea (CDAD).[6] If any of these reactions occurs, treatment needs to be immediately discontinued and further evaluation is needed.

Patients with known QT prolongation or receiving drugs with QT prolonging properties, ventricular arrhythmia, hypokalemia/hypomagnesemia, significant bradycardia, or taking Class IA or III antiarrhythmics should avoid taking vonoprazan triple pak.[6] If there are signs and symptoms of hepatitis, vonoprazan triple therapy should be discontinued. Evaluation of other medications is needed due to multiple severe drug-drug interactions and adverse reactions, discussed in the contraindications section, with the use of clarithromycin. Exacerbation of myasthenia gravis has also been reported in patients receiving clarithromycin.[6]

Contraindications

Vonoprazan dual and triple pak with known hypersensitivity to any of its components including vonoprazan, amoxicillin; or any other B-lactam antibiotic like penicillin and cephalosporins; or clarithromycin; or any other macrolide antibiotic like erythromycin; is contraindicated.[6] Moreover, vonoprazan reduces intragastric acidity which may alter absorption of antiretroviral drugs; thus concomitant use of rilpivirine-containing products and vonoprazan dual and triple pak is contraindicated due to the changes in the safety and/or effectiveness of the antiretroviral.[6]

Clarithromycin is a strong CYP3A inhibitor which may increase exposure and toxicity of CYP3A substrates. One of the CYP3A substrates is pimozide, an antipsychotic drug, is contraindicated with the concomitant use of clarithromycin due to increased risk of somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic malignant syndrome, or cardiac arrythmias.[6] Lomitapide, lovastatin, and simvastatin use with clarithromycin is also contraindicated. The concomitant use of ergot alkaloids increase the risk of vasospasm and ischemia of the extremities and other tissues including the central nervous system.[6] On top of CYP3A inhibition, clarithromycin is also a p-glycoprotein (P-gp) efflux transporter inhibitor; thus the administration of colchicine, a CYP3A and P-gp substrate, and clarithromycin in combination is contraindicated.[6] Lastly, vonoprazan triple pak is contraindicated in patients with history of cholestatic jaundice or hepatic dysfunction associated with prior use of clarithromycin.[6]

Adverse Drug Reactions

Diarrhea was the highest reported adverse reaction; 5.2% of patients taking vonoprazan dual pak and in 4% of patients taking vonoprazan triple pak reported diarrhea compared to 9.9% in lansoprazole triple therapy patients.[5] Dysgeusia also included a taste disorder; however, that can be related to patients with SARS-

Figure 1 | Secondary Outcomes Efficacy Assessments[5]

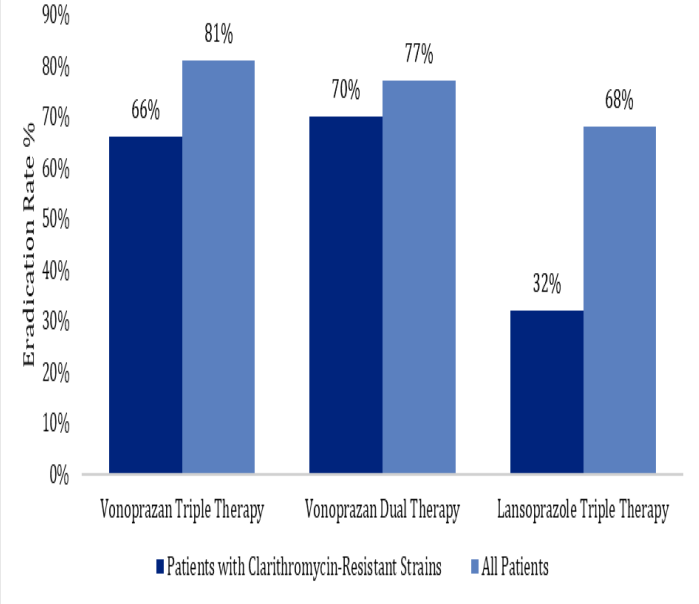
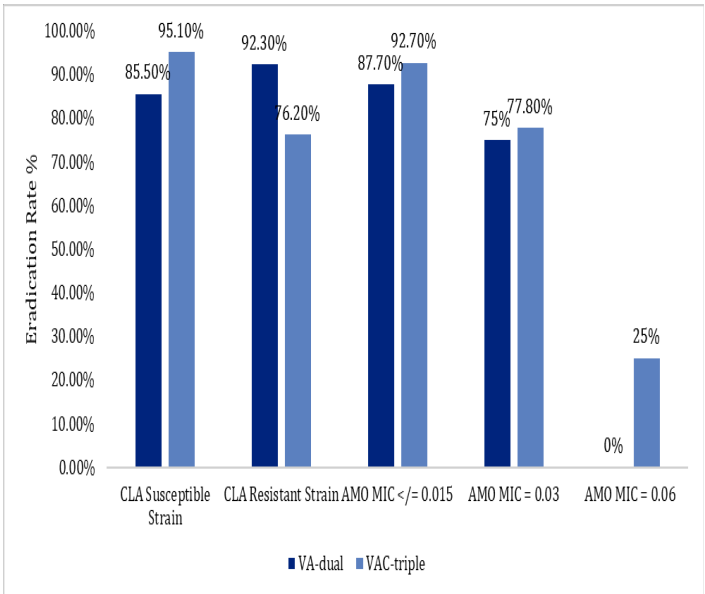


Figure 2 | Secondary Endpoints Summary, Clarithromycin (CLA) Susceptibility, and Amoxicillin (AMO) MIC Value[7]



CoV-2 infection. 2% of vonoprazan dual pak patients, 1.2% of vonoprazan triple pak patients, and 1.7% of lansoprazole triple therapy have reported COVID-19 infection.[5] Refer to **Table 4** for detailed summary of all adverse reactions reported in the clinical trial.

Pregnancy & Lactation

Special Populations

Vonoprazan Triple Pak is not recommended in pregnant women except in clinical circumstances where no alternative therapy is appropriate. The use of clarithromycin can cause embryo-fetal toxicity which leads to increased risk of miscarriage and incidence of fetal malformations. There are no adequate and well controlled studies of vonoprazan dual pak effects on pregnancy.[6]

There is potential risk of adverse liver effects shown in animal studies with vonoprazan and its metabolite presence in rat milk. Due to the potential risk, breastfeeding women should pump and discard milk for the duration of vonoprazan dual and triple pak until 2 days after therapy termination.[6]

Male Fertility Effects

Clarithromycin in vonoprazan triple pak may impair fertility in males of reproductive potential.[6]

Renal Impairment

Amoxicillin and clarithromycin are substantially excreted by the kidneys. Avoid the use of vonoprazan dual and triple pak in patients with severe renal impairment (eGFR<30 mL/min).[6]

Hepatic Impairment

Vonoprazan is metabolized to inactive metabolites via cytochrome P450 along with sulfo- and glucuronosyl-transferases. Avoid the use of vonoprazan dual and triple pak in patients with moderate to severe hepatic impairment (Child-Pugh B or C).[6]

Antimicrobial Resistance

Vonoprazan dual and triple therapy has shown effectiveness as a breakthrough therapy for H. pylori, but antimicrobial resistance is a concern when using amoxicillin and clarithromycin. Amoxicillin has not been a highly effective treatment with PPIs due to its need of high intragastric pH to exert its bactericidal effects. Moreover, resistance against clarithromycin arises when it fails to bind to the bacterial 50S ribosomal subunit thus failing to inhibit bacterial protein synthesis.[8] Vonoprazan has no effect on clarithromycin binding, but its ability to maintain a high intragastric pH increases the bactericidal effects of amoxicillin.[9] According to the Journal of Gastroenterology and Hepatology[8], the cure rates with vonoprazan triple therapy in the Japanese population was 92% in clarithromycin-susceptible patients while a cure rate of 80% was produced in clarithromycin resistant patients receiving vonoprazan dual therapy. However, 88% of patients received clarithromycin without benefit.[8] Although the vonoprazan triple therapy has been shown effective, this result is almost entirely due to the improved effectiveness of amoxicillin to treat H. pylori with almost no benefit from a second antibiotic like clarithromycin.[8]

Cost and Availability

Voquezna© dual and triple pak have the same retail price ranging from $232 to $246 based on the dispensing pharmacy. As

Table 4 | Common Adverse Effects & Incidence Rates by Treatment Arm[5]

Adverse Effect	Vonoprazan Dual (n=348)	Vonoprazan Triple (n=346)	Lansoprazole Triple (n=345)
Upper Abdominal Pain	2.6%	2.3%	2.9%
Diarrhea	5.2%	4.0%	9.9%
Nausea	1.7%	1.7%	2.6%
Dysgeusia	0.6%	4.3%	6.1%
Headache	1.4%	2.6%	1.4%

of now, in the United States, there are no generics available and vonoprazan is not sold as a single drug. Drug manufacturing co-pay assistance for patients is not available currently. A cost-effectiveness analysis of vonoprazan versus PPIs in the treatment of reflux esophagitis in China[10] showed that treatment of vonoprazan was associated with 0.02 quality-adjusted life years (QALYs) gained and a cost saving of $943. This shows that vonoprazan alone has the potential to cost-effectively treat other acid related disease states like acid reflux and esophagitis.

Clinical Implications

H. Pylori infection is becoming increasingly difficult to treat due to antibiotic-resistant strains. Treatment of H. pylori mainly consists of PPI-based triple therapy with clarithromycin, amoxicillin, or metronidazole.[4] Eradication rates still are below 80% in Europe and the Unites States due to rising clarithromycin resistance.[5] Based on the American College of Gastroenterology H. pylori infection treatment guidelines[4], clarithromycin based regimens should only be used in patients without prior macrolide use where clarithromycin resistance prevalence is less than 15%. Therefore, more effective therapies and a longer duration of therapy are needed due to frequent triple therapies failures.

Intragastric pH influence the effectiveness of antibiotics as well as H. pylori's replication and resistance. PPI might not be as effective in controlling intragastric pH sustainably.[5] Vonoprazan is a potassium-competitive acid blocker recently approved for H. pylori treatment as a dual therapy with amoxicillin or as triple therapy with amoxicillin and clarithromycin. Vonoprazan can sustainably maintain high gastric pH level which improved bactericidal activity of amoxicillin against H. pylori.[11] Amoxicillin is a broad-spectrum penicillin that inhibits the synthesis of bacterial cell wall by binding to the penicillin-binding proteins. Clarithromycin is a macrolide that blocks bacterial protein synthesis, however vonoprazan has no effect on the effectiveness of the antimicrobial effects of clarithromycin.

According to the clinical trial by William D. Chey et al.[6], the newly approved vonoprazan dual and triple therapies showed noninferiority to lansoprazole triple therapy for the eradication of H. pylori in patients not resistant to clarithromycin and amoxicillin, refer to **Table 3**. As shown in **Figure 1**, vonoprazan dual and triple therapies showed superiority to lansoprazole triple therapy with higher eradication rates in clarithromycin-resistant strains and all patients in the secondary analysis.[6] Clarithromycin-resistant strains were present in 22.2% of participants and had the lowest eradication rate with lansoprazole triple therapy indicating that clarithromycin-based regimens should not be used empirically in the United States.

The results from the United States and Europe clinical trial align with Japanese studies results of higher H. pylori eradication

rates when using vonoprazan-based regiment over PPI-based regimen. In the Japanese study performed by Suzuki et al.[7], the 7-day vonoprazan and low dose amoxicillin dual therapy provided acceptable H. pylori eradication rates and a similar effect to vonoprazan-based triple therapy in regions with high clarithromycin resistance, refer to **Figure 2**. Some of these results might have been impacted by Japan's differing prevalence of CYP2C19, impacting PPIs, and CYP3A4/5 variations, impacting vonoprazan. The slower the CYP enzyme metabolism is due to mutations the higher the effects of PPIs and vonoprazan on intragastric pH.[6] Also Japan's treatment duration is half of the United State and Europe's may also contribute to different outcomes.

To improve antimicrobial stewardship and decrease the use of antibiotics, it is important to optimize the current H. pylori regimens. Even though vonoprazan triple therapy was shown to be the most effective, vonoprazan dual therapy should be first utilized as it has higher eradication rates than lansoprazole triple therapy and only contains amoxicillin. In clarithromycin resistant patients, vonoprazan based regimen has shown to be more effective than PPI based regimen.[6] Nevertheless, most of the bactericidal effects are shown to be exerted by amoxicillin as it is more effective with vonoprazan in clarithromycin-resistant patients. Further studies are needed to show effectiveness of vonoprazan dual therapy in the United States possibly with a higher amoxicillin dose over adding clarithromycin.

Conclusion

The newly approved Voquezna dual and triple therapy has shown to be an effective treatment for the eradication of H. pylori. The addition of vonoprazan treatment is beneficial in PPI-resistant and clarithromycin-resistant patients as it improves acid suppression and the bactericidal activity of amoxicillin. In patients with previous macrolide exposure where the region's prevalence of clarithromycin resistance is over 15%, vonoprazan dual therapy should be utilized. With the introduction of vonoprazan in H. pylori treatment, further clinical trials are needed for other acid-related diseases.

References

1. Malaty, H M et al. "Transmission of Helicobacter pylori infection. Studies in families of healthy individuals." Scandinavian journal of gastroenterology vol. 26,9 (1991): 927-32. doi:10.3109/00365529108996244.
2. Nilius, M, and P Malfertheiner. "Helicobacter pylori enzymes." Alimentary pharmacology & therapeutics vol. 10 Suppl 1 (1996): 65-71. doi:10.1046/j.1365-2036.1996.22164007.x.
3. Berger, A. "Scientists discover how helicobacter survives gastric acid." BMJ (Clinical research ed.) vol. 320,7230 (2000): 268.
4. Fallone CA, Chiba N, Van Zanteri et al. The Toronto Consensus for Treatment of Helicobacter pylori infection in Adults. Gastro 2016; 15:51. Adapted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol 2017; 112:212. Copyright © 2017. www.nature.com/ajg.
5. Chey, William D et al. "Vonoprazan Triple and Dual Therapy for Helicobacter pylori Infection in the US and Europe: Randomized Clinical Trial." Gastroenterology, S0016-5085(22)00609-6. 6 Jun. 2022, doi:10.1053/j.gastro.2022.05.055.
6. Voquenzna Triple Pak (vonoprazan, amoxicillin, and clarithromycin) [prescribing information]. Buffalo Grove, IL: Phathom Pharmaceuticals.
7. Suzuki, Sho et al. "Seven-day vonoprazan and low-dose amoxicillin dual therapy as first -line Helicobacter pylori treatment: a multicentre randomised trial in Japan." Gut vol. 69,6 (2020): 1019-1026. doi:10.1136/gutjnl-2019-319954.
8. Graham, David Y et al. "Vonoprazan-containing Helicobacter pylori triple therapies contribution to global antimicrobial resistance." Journal of gastroenterology and hepatology vol. 36,5 (2021): 1159-1163. doi:10.1111/jgh.15252.
9. Mori, Hideki, and Hidekazu Suzuki. "Role of Acid Suppression in Acid-related Diseases: Proton Pump Inhibitor and Potassium-competitive Acid Blocker." Journal of neurogastroenterology and motility vol. 25,1 (2019): 6-14. doi:10.5056/jnm18139.
10. Wang, Zhenhua et al. "Cost-effectiveness analysis of vonoprazan versus proton pump inhibitors in the treatment of reflux esophagitis in China." Annals of translational medicine vol. 10,8 (2022): 480. doi:10.21037/atm-22-1722.
11. Takeuchi, Toshihisa et al. "Randomised trial of acid inhibition by vonoprazan 10/20 mg once daily vs rabeprazole 10/20 mg twice daily in healthy Japanese volunteers (SAMURAI pH study)." Alimentary pharmacology & therapeutics vol. 51,5 (2020): 534-543. doi:10.1111/apt.15641.

Personalized Medicine Corner

Evaluating the Clinical Effect of CYP2C19 Polymorphisms in Clopidogrel Use for Patients with Peripheral Artery Disease

Khoa Nguyen, PharmD

Peripheral artery disease, commonly caused by atherosclerosis, impacts the lower extremities by narrowing vessels. In the US, approximately 6.5 million people aged greater than 40 years suffer from this disease. Current American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend clopidogrel (75mg per day) or aspirin monotherapy for risk reduction. Clopidogrel is a prodrug that requires hepatic biotransformation to form an active metabolite. CYP2C19 is one of the enzymes involved in this biotransformation process. Therefore, the effectiveness of clopidogrel can be influenced among individuals with poor or intermediate metabolizers of CYP2C19. However, there is a lack of clear recommendations on CYP2C19 genetic testing for clopidogrel use. This review evaluated current evidence on the association between CYP2C19 polymorphisms and clinical effectiveness in PAD patients.

From EMBASE, PubMed, and Web of Science from inception to September 2020, this study reviewed 597 related articles and identified four relevant studies (2 prospective and two retrospective cohort studies) which assessed the effect or association of CYP2C19 polymorphisms with PAD clinical ineffectiveness. All four studies found a higher risk of reduced clinical effectiveness in patients with a CYP2C19 loss of function alleles (*2, *3). These results suggest the need for CYP2C19 genetic results for clopidogrel use in PAD patients. Preemptive genetic testing for CYP2C19 can help clinician decide on clopidogrel therapy and alternative agents, which is limited (only aspirin or clopidogrel is recommended, and ticagrelor is only recommended for patients with both PAD and CAD). Limitations of this review include a lack of randomized controlled trials on PAD populations, a small number of included studies with unique designs in outcomes, measurement, and stratified cohorts (authors were not able to pool all data for a meta-analysis.)

Overall, the authors recommended clinicians expand the use of CYP2C19 testing beyond CAD patients to include the PAD population, especially at locations where CYP2C19 testing is already established, to improve the effectiveness of clopidogrel therapy.

References

1. Díaz-Villamarín, X., et al., Genetic polymorphisms influence on the response to clopidogrel in peripheral artery disease patients following percutaneous transluminal angioplasty. Pharmacogenomics, 2016. 17(12): p. 1327-38.
2. Guo, B., et al., Patients carrying CYP2C19 loss of function alleles have a reduced response to clopidogrel therapy and a greater risk of in-stent restenosis after endovascular treatment of lower extremity peripheral arterial disease. J Vasc Surg, 2014. 60(4): p. 993-1001.
3. Pastromas, G., et al., Clopidogrel responsiveness in patients undergoing peripheral angioplasty. Cardiovasc Intervent Radiol, 2013. 36(6): p. 1493-1499.
4. Lee, J., et al., CYP2C19 Polymorphism is Associated With Amputation Rates in Patients Taking Clopidogrel After Endovascular Intervention for Critical Limb Ischaemia. Eur J Vasc Endovasc Surg, 2019. 58(3): p. 373-382.

Drug Update:
New Indications and Dosage Forms
August 2022

Jynneos® Intradermal Vaccine
New formulation: Approved for the prevention of smallpox and monkeypox under emergency use authorization; administered in a 2-dose series, maximum 28 days apart; the vaccine may be given in three ways:

- If you are 18 years or older, you may be given the vaccine into the skin layers of your forearm (like a tuberculosis skin test)
- If you are younger than 18 years or have a history of developing keloid scars, you may be given the vaccine in your upper arm (like the influenza shot)
- For infants under 12 months old, it can be given in the thigh like other vaccines they may have received (like the measles, mumps, rubella (MMR) shot)

Auvelity® (extended-release dextromethorphan and bupropion) Tablet
New formulation: Indicated for the treatment of major depressive disorder in adults functioning through antagonism of the NMDA receptor

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida