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Treating *Helicobacter pylori* Infection With Vonoprazan, A Potassium-Competitive Acid Blocker: A New Paradigm

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STRUCTURED ABSTRACT

Question: Are vonoprazan triple (Voquezna TriplePak) and dual regimens (Voquezna DualPak) non-inferior to standard lansoprazole-based triple regimen (Prevpac) for treatment-naïve individuals with *Helicobacter pylori* infection?

Design: Phase III, multicenter, double-blind randomized controlled trial.

Setting: Patients from 103 sites in the US, United Kingdom, Bulgaria, the Czech Republic, Hungary, and Poland.

Patients: Included patients were: (a) ≥ 18 years old; (b) indication to test for *H. pylori*, including dyspepsia, recent diagnosis of non-bleeding peptic ulcer, history of peptic ulcer with no prior treatment

of *H. pylori*, or requirement for long-term NSAID use; (c) positive ^{13}C-urea breath test for *H. pylori* infection; and (d) no prior treatment for *H. pylori* infection. All eligible patients then underwent eophagogastroduodenoscopy with biopsy for culture and antimicrobial susceptibility testing as well as histology. All study patients had active *H. pylori* infection confirmed by culture or histology.

Interventions/Exposure: Eligible patients were randomized 1:1:1 to open-label vonoprazan dual therapy (vonoprazan 20 mg b.i.d. plus amoxicillin 1g t.i.d X 14 days) vs double-blind vonoprazan triple therapy (vonoprazan 20 mg b.i.d. plus amoxicillin 1 g b.i.d. plus clarithromycin 500 mg b.i.d. X 14 days) vs lansoprazole triple therapy (lansoprazole 30 mg b.i.d. plus amoxicillin 1 gm b.i.d. plus clarithromycin 500 mg b.i.d. X 14 days).

Outcome: The primary endpoint was *H. pylori* eradication based on negative ^{13}C-urea breath test obtained at least 4 weeks after last dose of study medication. Patients with persistent *H. pylori* infection underwent repeat eophagogastroduodenoscopy with repeat antimicrobial susceptibility testing. Per FDA guidance, the primary non-inferiority endpoint was assessed in the study patients with *H. pylori* strains that were not resistant to clarithromycin or amoxicillin. Pre-determined secondary endpoints assessed frequency of *H. pylori* eradication in all study patients and frequency of eradication in study patients with clarithromycin-resistant strains of *H. pylori*.

Data Analysis: Modified intention-to-treat analysis and per-protocol analysis (defined as patients who took $\geq$ 75% of study drug) was performed for the primary endpoint and both secondary endpoints. Analyses were conducted in a hierarchical order for each comparison: vonoprazan dual therapy vs lansoprazole triple therapy and vonoprazan triple therapy vs lansoprazole triple therapy for non-inferiority of *H. pylori* eradication among patients with strains that were susceptible to clarithromycin and amoxicillin. Again, this analysis was guided by the US Food and Drug Administration (FDA). Secondary endpoints were

then assessed using superiority analysis for clarithromycin-resistant strains and for all patients.

Funding: Phathom Pharmaceuticals, manufacturer of vonoprazan.

Results: From December 2019 through January 2021, 3,385 patients were screened for eligibility, 1,046 were randomized, and 992 were fully evaluated (mean age: 51-52 years old; 37% male; 90% White; 42% from US; 98% with dyspepsia as indication to test for *H. pylori*; 20% with clarithromycin-resistant strains; 1% with amoxicillin-resistant strains; 63% with metronidazole-resistant strains). For the primary endpoint requested by the FDA, vonoprazan dual therapy and vonoprazan triple therapy were non-inferior to lansoprazole triple therapy for eradication of *H. pylori* with no resistance to clarithromycin or amoxicillin (78.5% vs 84.7% vs 78.8%, respectively) (**Figure 1**). Vonoprazan dual therapy and vonoprazan triple therapy were superior to lansoprazole triple therapy for *H. pylori* eradication when evaluating all patients (77.2% vs 80.8% vs 68.5%, respectively, $P < 0.01$) and when evaluating patients with clarithromycin-resistant strains (69.6% vs 65.8% vs 31.9%, respectively, $P < 0.001$). (**Figure 1**)

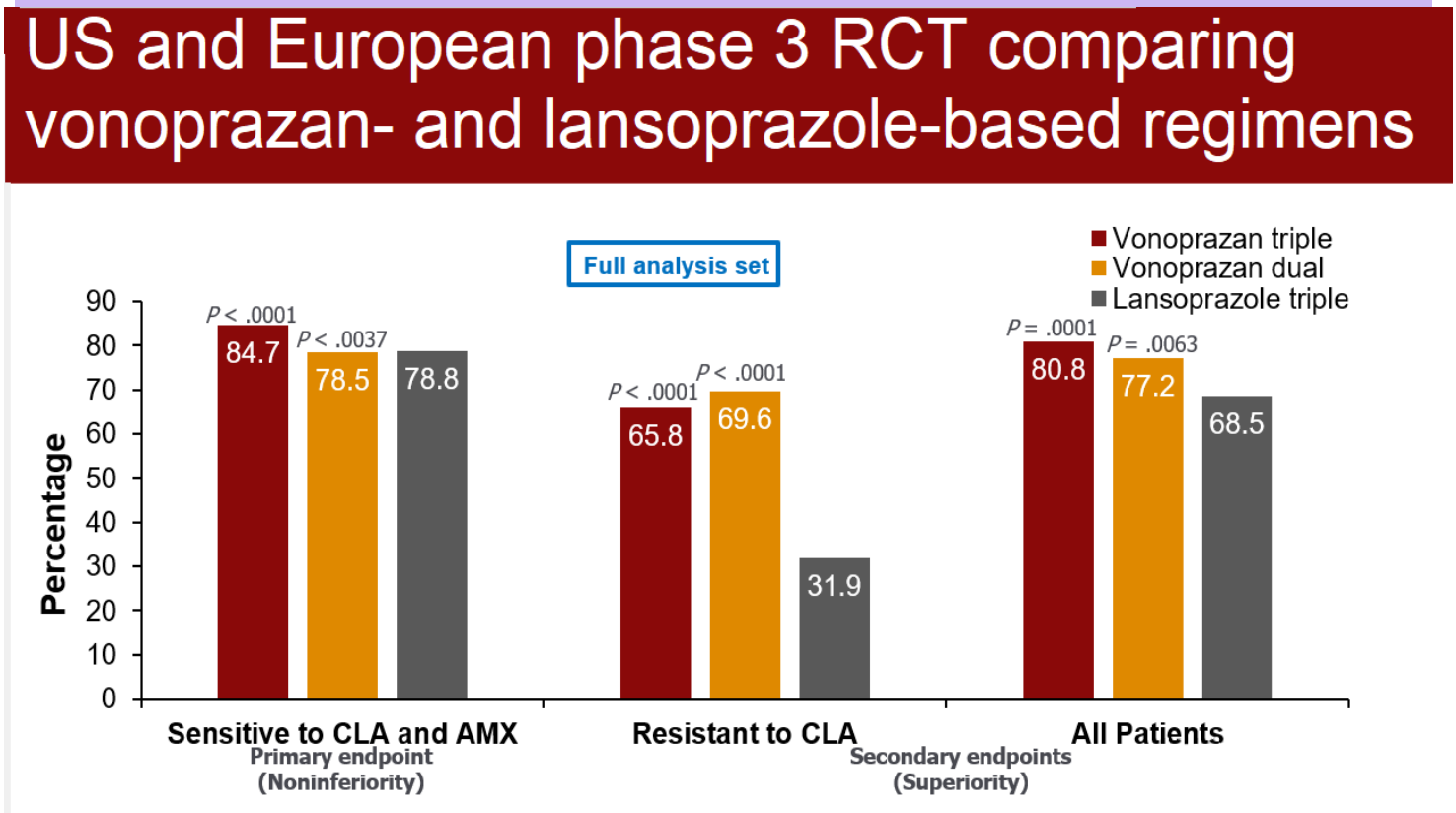

Figure 1: *Helicobacter pylori* eradication rates.
AMX, amoxicillin ; CLA, clarithromycin; RCT, randomized controlled trial.

COMMENTARY

Why Is This Important?

Quite simply, lansoprazole-based triple therapy with clarithromycin should not be used unless antimicrobial sensitivity testing has confirmed clarithromycin-sensitivity.[1] This is because lansoprazole-based triple therapy with clarithromycin and similar regimens only achieve 30% eradication rates in clarithromycin-resistant strains, and rates of clarithromycin resistance exceed 20% in most parts of the US. As seen in this study, this translates to successful eradication in only about 65%-70% of US patients with lansoprazole-based triple therapy with clarithromycin, which is far from optimal. Nevertheless, US database studies estimate that lansoprazole-based triple therapy with clarithromycin and similar regimens account for almost 50% of prescriptions.

Bismuth-based quadruple therapy and rifabutin-based triple therapy (Talicia) for 14 days are preferred regimens.[1,2] Unfortunately, compliance and pill burden make bismuth-based quadruple therapy regimens cumbersome and use of rifabutin-based therapy seems to have been limited by cost, limited formulary availability, co-pays, and lack of awareness. Therefore, the recent FDA approval[3] of vonoprazan-based dual therapy and vonoprazan-based triple therapy for *H. pylori* treatment are welcome.

Vonaprazan, a potassium-competitive acid blocker, produces earlier and more potent acid suppression than conventional proton pump inhibitors and this translates to more successful treatment of *H. pylori*. Specifically, enhanced gastric acid suppression optimizes the activity of amoxicillin and clarithromycin, which may be destabilized by lower pH. Also, active bacterial replication of *H. pylori* increases at higher gastric pH and this replication facilitates antibiotic eradication.

Key Study Findings

Vonoprazan dual therapy and vonoprazan triple therapy were superior to lansoprazole triple therapy for *H. pylori* eradication when evaluating all patients (77.2% vs 80.8% vs 68.5%, respectively, $P < 0.01$) and when evaluating patients with clarithromycin-resistant strains (69.6% vs 65.8% vs 31.9%, respectively, $P < 0.001$). (**Figure 1**)

Caution

Since only treatment-naïve *H. pylori* patients were enrolled, this study doesn't provide data about management of patients with refractory *H. pylori* infections. Otherwise, this is a very well-designed, Phase III RCT, which met all FDA requirements and led to FDA approval of vonoprazan-based dual therapy and triple therapy regimens.

My Practice

At my VA Medical Center, my current preferred therapy is bismuth -based quadruple therapy and I'm limited by my formulary to only using rifabutin-based triple therapy for salvage therapy in patients with refractory *H. pylori* infection.

Vonoprazan-based dual therapy with amoxicillin is ideal for good antibiotic stewardship.[4] If cost and availability concerns can be addressed at my VA Medical Center, then this will be my preferred first-line therapy.

It's also worth emphasizing the ACG Guideline recommendation that post-treatment testing should be performed routinely to ensure successful eradication.[2] I prefer to do this with stool antigens for *H. pylori* and have the specimen collected at least 4 weeks after completing antibiotics and 2 weeks after discontinuing acid suppression therapy.

For Future Research

Future studies should assess real-world efficacy of vonoprazan-based therapies in patients with refractory *H. pylori* infection. Additional studies should use next-generation sequencing[5] or other tools to better define rates of antibiotic-resistant strains in different geographic regions of the US.[5] Quality improvement research should also assess interventions to improve frequency of testing for eradication 4 weeks after patients complete treatment.

Conflict of Interest

Dr. Schoenfeld reports being an advisory board member and consultant for Phathom Pharmaceuticals.

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