Sequential Therapy Outperforms the Current Standard of Care for *Helicobacter pylori* Eradication

Vaira D, Zullo A, Vakil N, et al. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori *eradication: a randomized trial. Ann Intern Med 2007;146:556–63.*

Study Overview

Objective. To compare a 10-day sequential treatment regimen with standard 3-drug therapy for eradication of *Helicobacter pylori*.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. 300 patients were enrolled if they were referred to 1 of 2 Italian hospitals for a gastroenterology consultation for dyspepsia or peptic ulcers. Patients had to be aged ≥ 18 years and never treated for *H. pylori* infection. Those who failed previous *H. pylori* eradication therapy or had recently used antibiotics, proton pump inhibitors, histamine$_2$-receptor antagonists, or bismuth were excluded.

Intervention. Participants were randomized to either a 10-day sequential regimen (n = 150; twice-daily pantoprazole 40 mg, amoxicillin 1 g, and placebo for the first 5 days; followed by twice-daily pantoprazole 40 mg, clarithromycin 500 mg, and tinidazole 500 mg for the remaining 5 days) or standard therapy (n = 150; twice-daily pantoprazole 40 mg, clarithromycin 500 mg, and amoxicillin 1 g for 10 days).

Main outcome measure. The primary outcome measure was eradication of *H. pylori* infection, as determined by radiolabeled urea breath test. If the urea breath test was positive, patients underwent endoscopy for evaluation and to obtain biopsy specimens for histologic testing, bacterial culture, and assessment for antibiotic resistance.

Main results. Patients who received sequential therapy had a significantly greater eradication rate as compared with patients who received standard therapy in the intention-to-treat analysis (89% vs. 77%; difference, 12% [95% confidence interval {CI}, 3%–20%]; P = 0.0134), the modified intention-to-treat analysis (91% vs. 78%; difference, 13% [95% CI, 5%–21%]; P = 0.0022), and the per-protocol analysis (93% vs. 79%; difference, 14% [95% CI, 6%–21%]; P = 0.0013). In patients with clarithromycin-resistant strains (n = 43), infection was eradicated in 88.9% of those who received sequential therapy as compared with 28.6% of those who received standard therapy (difference, 60.3% [95% CI, 28.2%–75.9%]; P = 0.0034). Patients with metronidazole-resistant strains (n = 72) who received sequential therapy had a statistically significantly higher eradication rate as compared with those who received standard therapy (94.3% vs. 80%; P = 0.009). The incidence of major and minor side effects did not differ between groups (17% in both groups). One patient (0.7%) in the standard therapy group discontinued treatment due to side effects.

Conclusion. Sequential therapy is more effective for eradicating *H. pylori* infection as compared with standard therapy. Patients with clarithromycin-resistant strains achieved higher cures rates with sequential therapy versus standard therapy.

Commentary

H. pylori infection is responsible for the majority of duodenal and gastric ulcers, and there is strong evidence that this infection also increases the risk of gastric cancer [1]. The prevalence of *H. pylori* infection is strongly correlated with socioeconomic conditions, with over 80% of the population in developing countries and 20% to 50% in industrialized nations affected [1]. Several combination therapies have been an effective standard of treatment; however, resistance rates have been rising and eradication failures have increased to 1 in 5 patients [2]. Previous trials examining sequential therapy were unblinded and performed in an elderly or pediatric population [3,4]; thus, Vaira and colleagues engaged this randomized controlled trial to determine the effect of sequential therapy in an adult population with dyspepsia or peptic ulcers.

This study found that sequential therapy more effectively eliminated *H. pylori* infection as compared with standard 3-drug therapy. Subgroup analysis also showed an advantage with sequential therapy in patients with clarithromycin- or metronidazole-resistant bacteria; however, the small sample size limits the usefulness of these data. Further, because *H. pylori* resistance and infection prevalence rates vary between countries (and perhaps between locales, depending on the immigrant population), results of this trial performed in Italy may not be applicable to the United States. Also, exclusion criteria specifically prevented those

who had failed prior *H. pylori* eradication therapy or had been on acid-reducing regimens from participating in the study; this population should be addressed in future trials. Lastly, this trial does not elucidate the mechanism by which the sequential regimen performed better than the standard regimen; the improvement could be simply attributed to the use of tinidazole, an antibiotic that is not included in the standard regimen.

Applications for Clinical Practice

The 4-drug sequential regimen outperformed the standard regimen for eradicating *H. pylori* infection. However, the complexity of the regimen, the potentially different prevalence rates of *H. pylori* between countries, and the addition of the new antibiotic are all hurdles to overcome before widespread adoption should be advocated.

—Review by Mark S. Horng, MD, MPH

References

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