CLINICAL—ALIMENTARY TRACT

Efficacy of 5-Day Levofloxacin-Containing Concomitant Therapy in Eradication of *Helicobacter pylori* Infection

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of the CME activity, successful learners will be able to formulate an appropriate treatment schedule for eradication of *Helicobacter pylori* infection in infected patients naive to treatment.

See Covering the Cover synopsis on page 1; editorial on page 10.

BACKGROUND & AIMS: *Helicobacter pylori* have become resistant to antimicrobial agents, reducing eradication rates. A 10-day sequential regimen that contains levofloxacin was efficient, safe, and cost saving in eradicating *H pylori* infection in an area with high prevalence of clarithromycin resistance. We performed a noninferiority randomized trial to determine whether a 5-day levofloxacin-containing quadruple concomitant regimen was as safe and effective as the 10-day sequential regimen in eradicating *H pylori* in previously untreated patients. **METHODS:** We randomly assigned patients with *H pylori* infection to groups that were given 5 days of concomitant therapy (esomeprazole 40 mg twice daily, amoxicillin 1 g twice daily, levofloxacin 500 mg twice daily, and tinidazole 500 mg twice daily; n = 90) or 10 days of sequential therapy (esomeprazole 40 mg twice daily, amoxicillin 1g twice daily for 5 days followed by esomeprazole 40 mg twice daily, levofloxacin 500 mg twice daily, and tinidazole 500 mg twice daily for 5 more days; n = 90). Antimicrobial resistance was assessed by the E-test. Efficacy, adverse events, and costs were determined. **RESULTS:** Intention-to-treat analysis showed similar eradication rates for concomitant (92.2%; 95% confidence interval [CI], 84.0%–95.8%) and sequential therapies (93.3%; 95% CI, 86.9%–97.3%). Per-protocol eradication results were 96.5% (95% CI, 91%–99%) for concomitant therapy and 95.5% for sequential therapy (95% CI, 89.6%–98.5%). The differences between sequential and concomitant treatments were 1.1% in the intention-to-treat study (95% CI; −7.6% to 9.8%) and −1.0% in the per-protocol analysis (95% CI; −8.0% to 5.9%). The prevalence of antimicrobial resistance and incidence of adverse events were comparable between groups. Concomitant therapy cost $9 less than sequential therapy. **CONCLUSIONS: Five days of levofloxacin-containing quadruple concomitant therapy is as effective and safe, and less expensive, in eradicating *H pylori* infection than 10 days of levofloxacin-containing sequential therapy.**

Keywords: Bacterial Infection; Fluoroquinolone; Antibiotic Clinical Trial.

Helicobacter pylori is a transmissible human pathogen that causes symptomatic diseases, including adenocarcinoma of the distal stomach, in approximately 20% of infected subjects.[1,2] Therefore, this infection should be cured whenever it is diagnosed.[3] Although *H pylori* is susceptible to a number of antimicrobials, *H pylori* infection has proven challenging to cure because the prevalence of bacterial strains resistant to the most commonly used antimicrobials, in particular clarithromycin (CLA), increases.[4–6] As a result, currently recommended first-line therapies both in the United States and Europe achieve a 75%–80% eradication rate, which is not acceptable.[7,8] Because of this, the Maastricht III[9] and Maastricht IV (Dr Malfertheiner, personal communication, May 2011) Consensus Conferences recommended bismuth-containing quadruple therapy (ie, proton pump inhibitor [PPI] plus

Abbreviations used in this paper: AMO, amoxicillin; CI, confidence interval; CLA, clarithromycin; 5d-QCT, 5-day quadruple concomitant therapy; ITT, intention-to-treat; LEV, levofloxacin; MET, metronidazole; PP, per-protocol; PPI, proton pump inhibitor; ST, sequential therapy; 10d-ST, 10-day sequential therapy; TET, tetracycline; TIN, tinidazole; UBT, urea breath test.

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bismuth, tetracycline [TET], and metronidazole [MET]) as a first-line strategy in areas with a high (ie, >15%) prevalence of CLA resistance, even though compliance with this regimen is low.

A novel 10-day sequential therapy (ST) consisting of 5-day dual therapy (PPI standard dose twice daily plus amoxicillin [AMO] 1 g twice daily) followed by 5-day triple therapy (PPI standard dose twice daily plus CLA 500 mg twice daily plus tinidazole [TIN] 500 mg twice daily) has shown good eradication rates,[10,11] even when there is evidence of CLA resistance.[12] However, most recent studies have shown lower than expected efficacy with CLA-containing sequential regimens, thus raising the question as to whether this therapy should be recommended as an empiric first-line regimen.[13] In this regard, we have recently shown that in an area of high prevalence (ie, >15%) of CLA and dual (ie, CLA plus MET) resistance, a levofloxacin (LEV)-containing ST is more effective than a CLA-containing ST regimen, achieving eradication rates higher than 95%.[14] Among the alternative regimens to CLA-containing therapies, a novel bismuth-containing quadruple therapy using a single 3-in-1 capsule containing bismuth subcitrate, MET, and TET has recently been proposed to decrease the pill burden and improve patient compliance.[15] In a randomized clinical trial, this single-capsule bismuth-containing 10-day treatment showed an intention-to-treat (ITT) cure rate of 80% and a per-protocol (PP) cure rate of 93%.[15]

ST is actually a quadruple therapy with 3 antimicrobials (ie, AMO, a macrolide/quinolone, and an imidazole) and an acid suppressive agent given in sequence over a 10-day period. Based on the hypothesis that the use of 3 antimicrobials rather than the sequential scheme of drug administration plays a major role in the efficacy of ST, we designed a study to assess whether the concomitant administration of a PPI, AMO, LEV, and TIN for 5 days might be as effective as the 10-day sequential administration of the same drugs at the same total dose of antimicrobials in *H pylori*–infected patients naïve to treatment. Secondary end points were to assess the influence of antimicrobial resistance on the outcome of eradication treatments, the incidence of adverse events, and the costs related to either regimen.

Patients and Methods

Design Overview

This was a prospective, randomized, controlled study. At baseline, patients were evaluated for inclusion and exclusion criteria and provided written informed consent. Patients were then randomly assigned to a treatment group and had a follow-up evaluation to assess the eradication rate of *H pylori* infection and adverse events. The study was performed according to Good Clinical Practice and the Declaration of Helsinki and was approved by the institutional ethical committee. All patients who had not been eradicated of the infection were offered a second gastroenterology consultation, a rescue therapy, and retesting.

A total of 468 consecutive patients with dyspepsia who were referred to our gastroenterology units for consultation between January and December 2011 were asked to participate in the study. *H pylori*–infected patients who were at least 18 years of age and who had never received *H pylori* eradication treatment were included in the study. Diagnosis of *H pylori* infection was based on positivity to ^{13}C urea breath test (^{13}C-UBT) or on positivity to both rapid urease test and histology in those patients who underwent endoscopy because of age older than 45 years and/or presence of alarm symptoms. In patients undergoing endoscopy, 5 biopsy (2 antrum, 2 body, and 1 angulus) specimens were taken for histologic assessment according to the Sydney system and 2 more specimens (1 from the antrum and 1 from the body) were taken for rapid urease test. Two additional biopsy samples were obtained from the antrum for bacterial culture and antimicrobial susceptibility testing. Biopsy samples were sent to our microbiology laboratory within 24 hours and stored at −70°C. Isolated strains were tested for in vitro susceptibility to AMO, TET, CLA, LEV, and MET by E-test as described previously.[16–18] *H pylori* strains with a minimal inhibitory concentration value >0.25 mg/L, >1 mg/L, >0.5 mg/L, >2 mg/L, and >8 mg/L were considered to be resistant to AMO, TET, CLA, LEV, and MET, respectively. Exclusion criteria were previous treatment for *H pylori* infection; use of inhibitors of acid secretion and/or antibiotics during the 6 weeks before the study; gastrointestinal malignancy; previous gastroesophageal surgery; severe concomitant cardiovascular, respiratory, or endocrine diseases; clinically significant renal or hepatic disease; hematologic disorders; any other clinically significant medical condition that could increase risk; history of allergy to any of the drugs used in the study; pregnancy or lactation; alcohol abuse; drug addiction; severe neurologic or psychiatric disorders; and long-term use of corticosteroids or anti-inflammatory drugs.

Patients were enrolled by the medical personnel of the GI Unit after assessment of appropriate indication and ruling out any contraindication to the treatments. Patients were randomly allocated to receive one of the 2 treatment regimens using a centralized computer-generated random number list with block size of 3, 6, 9, and 12. An independent medical staff member assigned subjects to the 2 schedules. In each block there were serially numbered, sealed, opaque envelopes. Each patient received the next pack stored in the center following ascending order of labels. Patients were interviewed at completion of therapy to assess adherence to the therapeutic regimen and adverse events by medical personnel blinded to the eradication regimen of each patient. In particular, first open-ended questions on adverse effects and then specific questions on anticipated adverse events were asked. To assess whether the infection had been eradicated, *H pylori* status was reevaluated by ^{13}C-UBT performed by nonmedical personnel unaware of the eradication regimen of each patient at 6 and 10 weeks after completion of therapy. Infection was considered eradicated if patients had a negative test result on both occasions.^{13}C-UBT was performed after an overnight fast. A baseline breath sample was obtained, and 100 mg of ^{13}C urea with citric acid (1.4 g) was administered as an aqueous solution (Expirobacter; SOFAR, Milano, Italy). Another breath sample was collected 30 minutes later. The test result was considered positive if the difference between the baseline sample and the 30-minute sample exceeded 5.0 parts/1000 of $^{13}CO_2$. All breath tests were analyzed at the same laboratory by using a single gas isotope ratio mass spectrometer (ABCA, Europe Scientific, Crewe, England). All treated patients discontinued treatment with PPIs at least 2 weeks before under-