

A Comparison of 10 and 14 Days of Lansoprazole Triple Therapy for Eradication of *Helicobacter pylori*

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Background: Data from large, multicenter, US studies determining the efficacy of triple therapy for the eradication of *Helicobacter pylori* are lacking, especially for a treatment duration of less than 14 days.

Methods: Patients with *H pylori* infection and active duodenal ulcer disease or a history of duodenal ulcer disease within the past year were randomized to receive 30 mg of lansoprazole, 1 g of amoxicillin, and 500 mg of clarithromycin twice daily for 10 or 14 days. The primary efficacy end point was the eradication of *H pylori* as confirmed by negative histological and culture results at 4 to 6 weeks after the completion of treatment.

Results: Of 284 patients enrolled in the study from 46 US sites, 236 met the entry criteria. At 4 to 6 weeks after the end of therapy, *H pylori* was eradicated in 85% (96/113) of the patients receiving 14-day triple therapy and

in 84% (103/123) of those receiving 10-day triple therapy by per-protocol analysis (95% confidence interval for treatment group differences, -10.5 to 8.1; $P > .05$). There was also no significant difference between the 14- and 10-day treatment groups when analyzed by an intent-to-treat analysis of *H pylori* eradication. A similar proportion of patients in each treatment group reported an adverse event related to therapy (34% [46/136] vs 38% [56/148], respectively).

Conclusions: In patients with an active or a recent history of duodenal ulcer, lansoprazole-based triple therapy for 10 or 14 days is highly effective in the eradication of *H pylori*. The duration of therapy may be reduced from 14 to 10 days without a significant effect on regimen efficacy.

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CURE OF *Helicobacter pylori* infection has resulted in ulcer healing and a significant reduction in ulcer recurrence, thereby altering the natural history of ulcer disease.¹⁻⁷ In this context, numerous *H pylori* treatment regimens, including an antisecretory agent with 1 or 2 antibiotics, administered for 7 to 14 days have been evaluated.⁸⁻²⁵ Since consistently higher *H pylori* cure rates have been reported with proton pump inhibitor-based triple therapy, growing consensus favors this therapy over proton pump inhibitor-based dual therapy.²⁶

Recent investigation of triple anti-*H pylori* therapies has evaluated the effect of shortening the duration of treatment, thereby possibly increasing compliance, decreasing adverse effects, and lowering the cost of treatment. Promising results (*H pylori* eradication rates >90%) have been reported in European studies of triple therapy administered for 1 week,^{11-21,23-25} although the designs of most of these studies had limitations, such as only 1 *H pylori* detection

method (eg, ¹³C urea breath test), lack of an intent-to-treat analysis, and lack of a comparison of identical regimens for 14 days and less. In a single-center study, *H pylori* eradication and noncompliance increased directly with duration of twice-a-day triple therapy (86% and 0%, respectively, with 7 days of therapy; 90% and 6% with 10 days; and 92% and 10% with 14 days), although the study did not detect significant differences in efficacy between treatment groups, possibly owing to the small size of the individual treatment groups.²⁷ Thus, large multicenter studies conducted in the United States comparing a 14-day regimen with those of shorter periods (7 to 10 days) are still needed to identify the ideal duration for triple therapy.

We sought to further identify the optimal duration of triple therapy in a large, double-blind, multicenter, randomized study of patients with duodenal ulcer residing in the United States by comparing the efficacy of a 10- and a 14-day triple therapy regimen of lansoprazole, amoxicillin, and clarithromycin to eradicate *H pylori* infection.

PATIENTS AND METHODS

Patients who met the entry criteria, including being 18 years of age or older, having an active duodenal ulcer (primary lesion of ≥ 3 mm in diameter with visible depth) documented by endoscopy or a history of endoscopically documented duodenal ulcer disease within the past year, and being positive for *H pylori* as documented by positive results on a rapid urease test (CLOtest, Delta West Ltd, Perth, Western Australia) or histological detection in gastric biopsy specimens, were randomized to treatment. Patients were subsequently dropped from the study if the presence of *H pylori* determined by rapid urease test was not confirmed by histological findings and/or culture of biopsy specimens. Patients with coexisting gastric ulcer or erosive esophagitis, a history of gastroduodenal surgery, or other complications at the time of endoscopy were excluded, as were those using any antimicrobial agents within 2 weeks prior to initiating study treatment (or within 6 weeks if such use was for *H pylori* eradication) and those taking antiulcer drugs in dosages indicated for ulcer disease for more than 5 days within 2 weeks prior to study entry. Patients requiring anticoagulants or anti-inflammatory drugs were also excluded.

STUDY DESIGN

Patients were stratified according to their baseline duodenal ulcer status (active or historical) and were randomly assigned within each stratum to the 14- or 10-day treatment group. All study medication was matched with placebo to maintain the double-blind nature of the study. Patients self-administered 5 capsules (1 of lansoprazole [30 mg] or placebo and 4 of amoxicillin [250 mg] or placebo) and 1 tablet of study medication (clarithromycin [500 mg] or placebo) 2 times daily before breakfast and dinner for 14 days. Patients also received antacid tablets (Gelusil, Parke-Davis, Morris Plains, NJ; 0.4 g of magnesium and aluminum hydroxides and 25 mg of simethicone) and were instructed to use them only as needed for symptom relief. Patients were instructed to avoid antiulcer and ulcerogenic medication (except as noted above) and any antibiotic other than study drug or antacid from study

enrollment until completion of the study (final endoscopy, 4 to 6 weeks after treatment).

Compliance, symptoms, and adverse events were assessed by returned pill count and direct questioning at each treatment visit. Patients completed diaries on a daily basis during the acute phase of the study (through the week 6 visit), recording study drug dosing information, frequency of antacid consumption, and episodes of daytime and nighttime abdominal pain (defined as none, mild, moderate, or severe). Endoscopy with biopsy was repeated at least 4 weeks after treatment was completed (week 6 visit).

The study protocol was approved by the local Institutional Review Board of each of the 46 participating centers; all patients gave written informed consent.

DETERMINATION OF *H PYLORI* STATUS

Five biopsy specimens, 3 from the antrum and 2 from the greater curvature of the corpus (3 for histological examination and 2 for culture), were obtained at each endoscopy, which was performed at the screening and week 6 visits. At the screening visit only, an additional antral biopsy specimen was obtained for the rapid urease test, and a serum sample was collected for determining the presence of IgG antibodies to *H pylori* (FlexSure HP test, Smith-Kline Diagnostics Inc, San Jose, Calif).

Formalin-fixed, paraffin-embedded tissue sections were stained separately with hematoxylin-eosin for the evaluation of gastritis and Warthin-Starry stain to detect *H pylori*. All histological preparations were evaluated by a pathologist under the direction of one of us (M.H.). The examining pathologist was blinded to the patients' clinical status and treatment and to the results of other tests. Biopsy specimens were examined to assess the degree of gastritis, including acute and chronic inflammation, atrophy, and intestinal metaplasia, and graded semiquantitatively according to the Sydney system.²⁸ The density of the *H pylori* organisms was graded semiquantitatively using the following scale: grade 0, negative (no organisms seen); grade 1, mild (1 to a few organisms present in a single foveola in at least 1 biopsy sample, but in no more than 1 foveola); grade 2, moderate (multiple clusters of organisms in 1 foveola or organisms in more than 1 foveola, but in less than half of the foveola); and, grade 3, severe (numerous

RESULTS

Two hundred eighty-four patients were enrolled in the study based on positive rapid urease test results and were randomized to receive lansoprazole, amoxicillin, and clarithromycin twice daily for 10 ($n = 148$) or 14 days ($n = 136$). The treatment groups were well matched at baseline in relation to most demographic characteristics, duodenal ulcer status, and histological gastritis (**Table 1**). There was a significant difference between the treatment groups with respect to race: 61% of the patients in the 10-day treatment group were white, compared with 51% of the 14-day treatment group. Most patients (86% and 89% of patients in the respective treatment groups) had an endoscopically documented duodenal ulcer at baseline, and the majority of enrolled patients had

received previous therapy for gastrointestinal disorders (89% and 79% of patients in the 10- and 14-day treatment groups, respectively; $P < .05$). The presence of an endoscopically documented ulcer or a history of ulcer was established, and the presence of *H pylori* was confirmed by histologic examination and/or culture of biopsy specimens in 258 of the 284 patients. Because of various protocol violations (eg, no *H pylori* assessment at the week 6 visit, noncompliance, or other antibiotic usage), 236 of the 258 patients were included in the per-protocol analysis of *H pylori* eradication.

ERADICATION OF *H PYLORI*

Helicobacter pylori was eradicated from 103 (84%) of 123 patients in the 10-day treatment group and from 96 (85%)

organisms diffusely present in half or more foveolae in a single biopsy sample).

Biopsy specimens for culture were transported in modified Stuart transport media, inoculated to both selective and nonselective media, and incubated at 37°C in microaerobic conditions. The *H pylori* organisms were morphologically identified by Gram stain and the production of catalase, oxidase, and urease. Clarithromycin and amoxicillin (using ampicillin) susceptibility testing was performed using the epsilometer test (E-test, AB Biodisk, Solna, Sweden). Minimal inhibitory concentrations (MICs) of ≤ 0.5 $\mu\text{g/mL}$ and > 2 $\mu\text{g/mL}$ indicated susceptibility and resistance, respectively, to clarithromycin. An ampicillin MIC of ≤ 0.25 $\mu\text{g/mL}$ indicated susceptibility to amoxicillin; there are currently no known *H pylori* isolates resistant to amoxicillin. Microbiological testing was conducted at a central laboratory (Microbiology Specialists Inc, Houston, Tex) under the direction of 1 of us (A.W.).

At screening, the presence of *H pylori* was defined by at least 2 positive test results (rapid urease test and either histological examination and/or culture). A total of 22 patients were excluded from the efficacy analysis owing to a lack of *H pylori* organisms at baseline: 20 patients had *H pylori* documented by only 1 test; and *H pylori* was not documented by any test for the remaining 2 patients. Eradication was defined as both histological studies and cultures being negative for *H pylori* organisms at least 4 weeks after the end of treatment.

STATISTICAL ANALYSIS

Equivalence of the 2 treatment groups was evaluated according to criteria developed by the Anti-Infective Division of the Food and Drug Administration. These criteria required that the absolute value of the lower bound of the 95% confidence interval for the difference between treatments not exceed 15% if the eradication rate for the better of the 2 treatment groups was between 80% and 89%.

A sample size of at least 260 (130 patients in each treatment group) was chosen to achieve at least an 80% chance that the absolute value of the lower bound of the 95% confidence interval for the difference between the 2 treatment groups in *H pylori* eradication rates at the week 6 visit (4 to 6 weeks after the completion of treatment) did not

exceed 15%, assuming the true eradication rate of the better of the 2 treatment groups was 85% and that the difference between the true eradication rates was no greater than 3%.

A per-protocol analysis and a more conservative (worst case), intent-to-treat analysis, which included patients with missing data as failures, were conducted for *H pylori* eradication. Patients who prematurely discontinued taking study medication owing to a treatment-related adverse event, who were considered a therapeutic failure, or who required an antiulcer or antireflux drug were included in the per-protocol analysis of *H pylori* eradication, and patients who prematurely discontinued treatment because of 1 of these reasons and were missing the posttreatment *H pylori* eradication assessment were included in the analysis as treatment failures (6 patients in this study). An intent-to-treat analysis was performed for gastritis and patient diary data.

The comparability of the treatment groups was assessed with respect to demographic variables and medical and social histories by the χ^2 test and 1-way analysis of variance. Baseline gastritis findings were compared among the treatment groups using Cochran-Mantel-Haenszel methodology for ordered response variables.

Differences between the treatment groups at the week 6 visit with respect to *H pylori* eradication were assessed using the Cochran-Mantel-Haenszel test, with baseline duodenal ulcer status (active or healed) and investigator's geographic region as stratification factors. Exact binomial 95% confidence intervals for *H pylori* eradication were constructed for each treatment group and for the difference in *H pylori* eradication rates between the treatment groups. The treatment groups were also compared after adjusting for concomitant factors using the Cochran-Mantel-Haenszel test.

Resolution or improvement of gastritis from baseline to the week 6 visit was assessed using the Cochran-Mantel-Haenszel test. The mean severity of daytime and nighttime abdominal pain, the percentage of days and nights with abdominal pain, the mean number of antacid tablets taken per day, and the percentage of days that antacid was used during the treatment and posttreatment periods were compared between treatment groups using the Wilcoxon 2-sample test. The Fisher exact test was used to compare the incidence of treatment-related adverse events (defined as possibly or probably related) between the treatment groups.

of 113 in the 14-day treatment group. The 95% confidence interval for the difference in *H pylori* eradication rates between the treatment groups (-0.5 to 8.1) supported the conclusion of equivalence of the 2 treatment groups based on the predefined criteria (**Table 2**). This observation was unaffected after adjustment for potentially influential factors, including investigator, sex, race, age, study drug compliance, baseline *H pylori* grade, baseline duodenal ulcer status (active or historical), baseline size of the index ulcer, and alcohol, tobacco, or caffeine use. By a worst-case intent-to-treat analysis, in which patients who failed to return for the follow-up evaluation were considered to have persistent *H pylori* infection, the *H pylori* eradication rates were 81% (110/135) and 82% (103/126), respectively, with the 95% confidence interval for the difference in *H pylori* eradication

rates between the 2 treatment groups (-9.7 to 9.1) also supporting the conclusion of equivalence.

ULCER STATUS

Among the evaluable patients enrolled with an active ulcer (n = 228), 166 did not have an ulcer at the final endoscopy, which was conducted 4 weeks after the completion of therapy. There was no statistically significant difference in ulcer status between the 10- and 14-day treatment groups.

RESOLUTION OF GASTRITIS

Patients experienced improvement or resolution of histological markers of chronic gastritis at the week 6 fol-

Table 1. Pretreatment Characteristics of Patients With Active or Recent History of Duodenal Ulcer Randomized to Receive Lansoprazole, Amoxicillin, and Clarithromycin for 10 or 14 Days*

Characteristic	10 Days (n = 148)	14 Days (n = 136)
Age, mean ± SD, y	50.7 ± 13.2	49.5 ± 14.6
Sex		
Female	57 (39)	41 (30)
Male	91 (62)	95 (70)
Race†		
White	91 (61)	69 (51)
Hispanic	26 (18)	33 (24)
Black	26 (18)	19 (14)
Other	5 (3)	15 (11)
Smoker‡	56 (38)	48 (35)
Alcohol use§	54 (37)	59 (43)
Active duodenal ulcer	127 (86)	120 (89)
Chronic gastritis with		
Acute inflammation	138 (93)	129 (95)
Chronic inflammation	147 (99)	133 (98)
Atrophy	5 (3)	3 (2)
Intestinal metaplasia	0 (0)	0 (0)

*All values other than age are expressed as number (percentage).

†P < .05.

‡Smoker defined as any usage of tobacco.

§Alcohol use defined as consumption of any quantity of alcohol on a routine basis.

low-up visit compared with the pretreatment visit. In an intent-to-treat analysis, no statistically significant differences were observed between the 10- and 14-day treatment groups in the percentage of patients showing resolution or improvement of acute inflammation (91% each [115/127] vs [107/117], respectively) and chronic inflammation (28% [36/128] and 21% [24/117], respectively). Among the few patients with atrophy at baseline, resolution of findings was observed for 6 of 7 patients. No patient had intestinal metaplasia at baseline or at the week 6 visit.

ANTIMICROBIAL SUSCEPTIBILITY

Helicobacter pylori was cultured before the initiation of treatment, and susceptibility data were available for 124 study patients. Culture and susceptibility data were not available for 137 patients (7 who had positive culture results but no susceptibility results and 130 patients who had negative culture results). Ninety-eight percent (122/124) of the isolates were susceptible to amoxicillin using the MIC criterion of ≤ 0.25 $\mu\text{g/mL}$. The MICs for the 2 isolates that were not within this range were 2 $\mu\text{g/mL}$ and > 256 $\mu\text{g/mL}$. Neither isolate was retested by the epilometer test. The agar dilution result for the isolate originally found to be 2 $\mu\text{g/mL}$ was 0.5 $\mu\text{g/mL}$; the second isolate was not available for agar dilution MIC testing. Thus, the purported resistance to amoxicillin could not be confirmed. Eighty-six percent (107/124) of the isolates were susceptible to clarithromycin.

Among the 107 patients infected with clarithromycin-susceptible isolates, *H pylori* was eradicated from 93% (53/57) and 96% (48/50) of the patients in the 10- and 14-day treatment groups, respectively. Among the 17 pa-

Table 2. *Helicobacter pylori* Eradication at 4 to 6 Weeks Posttreatment by Lansoprazole, Amoxicillin, and Clarithromycin Treatment Group*

	10 Days	14 Days
Per-protocol analysis		
% (n/N)	84 (103/123)	85 (96/113)
95% CI	76.0-89.8	77.0-91.0
95% CI for difference†	-10.5 to 8.1	
Intent-to-treat analysis		
% (n/N)	81 (110/135)	82 (103/126)
95% CI	73.9-87.6	73.9-88.1
95% CI for difference†	-9.7 to 9.1	

*CI indicates confidence interval.

†95% CI for difference refers to *H pylori* eradication rates between treatment groups.

tients with primary clarithromycin resistance, *H pylori* was eradicated from 1 of 6 patients in the 10-day therapy group and from 7 of 11 patients in the 14-day therapy group.

Development of antibiotic resistance during treatment with lansoprazole-based triple therapy was an infrequent occurrence. Of the 107 patients who had isolates susceptible to clarithromycin pretreatment, 2 were positive for *H pylori* and had susceptibility results at the week 6 visit. Neither of these patients had a persistent infection caused by clarithromycin-resistant organisms. Three patients in the 10-day treatment group and 1 patient in the 14-day treatment group who had no clarithromycin susceptibility results before treatment had an isolate resistant to clarithromycin after treatment. None of the patients with an amoxicillin-susceptible *H pylori* isolate developed resistance to amoxicillin after treatment.

RESOLUTION OF SYMPTOMS

After controlling for *H pylori* eradication status, no statistically significant differences were observed between the treatment groups for either the frequency or the mean severity of daytime or nighttime abdominal pain during the treatment period. Similarly, the treatment groups were comparable based on patients' consumption of antacid tablets during the study. However, a statistically significant difference was observed for the frequency and the mean severity of daytime abdominal pain during the follow-up period.

COMPLIANCE AND ADVERSE EFFECTS

At least 90% of patients in each of the treatment groups took more than 90% of their study medication. Twelve patients (2 and 10 in the 10- and 14-day treatment groups, respectively) took less than 70% of study medication; none and 7 of these patients in the respective treatment groups were excluded from the per-protocol analysis for *H pylori* eradication, and the remaining 5 patients were classified as failures. Nine patients discontinued taking the study medication prematurely at least in part because of drug-related adverse events (3 and 6 patients in the respective treatment groups).

The 2 treatment regimens were comparable based on the percentage of patients who reported a treatment-related adverse event: 38% (56/148) of the patients in the 10-day treatment group and 34% (46/136) of the patients in the 14-day treatment group. The most commonly reported events were diarrhea and taste disturbance, with no statistically significant differences between treatment groups for any specific drug-related adverse event. The majority of treatment-related adverse events experienced by study patients were mild or moderate in severity.

COMMENT

While the medical literature over the last decade is replete with *H pylori* treatment studies, the optimal duration of triple therapy, especially for US patients, has not been adequately evaluated, and consensus is lacking. Most comparisons have been based on results from separate, European trials that have used different methods, failed to use multiple diagnostic tests to document the presence of *H pylori* and verify eradication, and failed to include intent-to-treat analyses or enroll sufficient numbers to detect significant differences. This trial incorporated these important features to compare in a US study the efficacy and tolerability of lansoprazole-based triple therapy for 14 or 10 days.

Earlier research has demonstrated 14-day triple therapy with lansoprazole, clarithromycin, and amoxicillin to be effective in eradicating *H pylori* in up to 94% of patients.²⁹ When a rigorous Food and Drug Administration-directed analysis was used (that included patients as treatment failures who dropped out of the study after experiencing adverse events considered possibly or probably treatment related), the *H pylori* eradication rate with 14-day lansoprazole-based triple therapy was 92%.³⁰ The results of this study are similar for both a 10- and a 14-day regimen. The treatment groups were found to be comparable based on cure of *H pylori* infection, resolution or improvement of gastritis markers, frequency and mean severity of daytime or nighttime abdominal pain, patients' antacid use, and tolerability. Equivalent *H pylori* eradication rates were achieved when standard, 14-day triple therapy with lansoprazole, amoxicillin, and clarithromycin twice daily was shortened to 10 days (85% and 84%, respectively) (Table 2). The eradication rates for the respective treatment groups in the worst-case intent-to-treat analysis (82% and 81%) were similar to those from the per-protocol analysis, illustrating the robustness of lansoprazole-based triple therapy and the importance of including both analyses in order to compare results from different trials. Inclusion of patients without *H pylori* eradication data and classifying them as treatment failures in the intent-to-treat analysis resulted in high *H pylori* eradication rates that still compare favorably with the outcomes of dual therapy when it was studied under the least stringent study methodologies (eg, per-protocol analysis that excluded patients with missing data, patients who prematurely discontinued taking study medication or did not return for a posttreatment visit, and patients with an unhealed ulcer following the completion of treatment).

The *H pylori* eradication rates using the intent-to-treat analysis in this study are similar to those that have been reported with other proton pump inhibitor-based triple therapy, while per-protocol analysis rates are numerically lower.¹¹⁻²⁵ This difference between per-protocol efficacy is because patients who prematurely discontinued taking the study medication because of a treatment-related adverse event or who required an antiulcer or antireflux medication were included as therapeutic failures in the per-protocol analysis of our study. These types of patients have generally been excluded from efficacy evaluations in other studies of anti-*H pylori* treatment regimens, resulting in more favorable results. We included these patients in our analyses to more realistically simulate the efficacy of *H pylori* treatment that can be expected in clinical practice.

The 14% prevalence of primary clarithromycin resistance found in our study is higher than the 5% to 8% prevalence previously reported from studies conducted in the United States.^{31,32} As expected based on the results of others,³³ we found the *H pylori* eradication rate of a clarithromycin-containing triple therapy regimen is compromised in patients infected with a clarithromycin-resistant organism: *H pylori* eradication in 94% of patients infected with clarithromycin-susceptible strains and 47% of patients with clarithromycin-resistant strains. Our results are also consistent with those of Wurzer et al³⁴ and Schwartz et al,²⁹ who suggested that secondary clarithromycin resistance develops infrequently among patients treated with a proton pump inhibitor combined with clarithromycin and another antibiotic.

The results of our study as well as those from the study by Laine et al²⁷ suggest that twice-a-day triple therapy for 10 days leads to high rates of *H pylori* eradication, tolerability, and compliance. Thus, while 14-day therapy with lansoprazole, amoxicillin, and clarithromycin has recently received approval from the Food and Drug Administration, these and other results from ongoing research may eventually lead to a shorter, 10-day duration of treatment.

CONCLUSIONS

In patients with an active or a recent history of duodenal ulcer, lansoprazole-based triple therapy for 10 or 14 days is highly effective in the eradication of *H pylori* infection. The duration of therapy may be reduced from 14 days to 10 days without a significant effect on the regimen efficacy.

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