Randomized Controlled Trial Comparing Proton Pump Inhibitor-Based Eradication Regimen versus Low-Cost Eradication Regimen for Patients with *Helicobacter pylori* with Uninvestigated Dyspepsia

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DISCLOSURE
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ABSTRACT
Background: The impact of various *Helicobacter pylori* eradication regimens in patients with uninvestigated dyspepsia is controversial.

Objective: To compare symptom relief, tolerability, and treatment compliance among *H pylori*–positive subjects with uninvestigated ulcer-like dyspepsia treated with 2 widely used *H pylori*–eradication regimens.

Methods: Patients were randomized to a 2-week course of either bismuth subsalicylate, metronidazole, tetracycline, and cimetidine or lansoprazole, amoxicillin, and clarithromycin. Antacid tablets were taken as needed for pain and discomfort. Primary endpoints evaluated were symptom relief, medication compliance, tolerance, and *H pylori* eradication rates.

Results: Sixty of the 62 patients (mean age 50 years) enrolled completed the study. The patients treated with lansoprazole-based regimen consumed fewer antacid tablets (10.1 versus 27.2 tablets,

P=0.013) and were more compliant with their regimen (92.9% versus 62.1%, respectively, *P*=0.006). A greater incidence of moderate-to-severe adverse events was reported among the patients treated with the bismuth-based regimen when compared with the lansoprazole group (38.7% versus 13.8%, *P*=0.029). A 7-point gastrointestinal symptom rating scale was used. Symptoms in both groups improved significantly at 8 weeks compared to baseline (1.65 versus 1.18, *P*=0.0008). *H pylori* eradication was achieved in 86.8% of all patients.

Conclusions: Treatment with the lansoprazole-based *H pylori*–eradication regimen produced higher symptom relief and patient compliance compared with treatment with the bismuth-based regimen in *H pylori*–positive patients with uninvestigated dyspepsia.

INTRODUCTION

Helicobacter pylori is a common organism that infects approximately one third of all Americans and more than 50% of individuals worldwide.[1] Dyspepsia, defined by the Rome II criteria as "pain or discomfort centered in the upper abdomen," is also common and affects 15% to 20% of the adults, although only a fraction of these seek health care.[2-4] Substantial controversy surrounds the impact of *H pylori* eradication on the prevalence of dyspepsia symptoms.[5-8] Although randomized, controlled clinical trials have shown no or marginal benefits for patients with non-ulcer dyspepsia, other studies have suggested a reduction in symptoms and health care costs following the treatment of *H pylori* in patients with uninvestigated dyspepsia.[9,10]

Numerous regimens have been developed and approved by the Food and Drug Administration for the treatment of patients infected with *H pylori*. These regimens combine antimicrobial agents (including bismuth compounds) with an antisecretory agent such as a proton pump inhibitor (PPI) or a histamine-2 receptor antagonist (H2RA). While none of these therapies have been shown to produce *H pylori* eradication in 100% of patients, several regimens, and in particular the PPI-based triple therapy regimen (combination of a PPI with clarithromycin and amoxicillin) and the BMT quadruple regimen (combination of bismuth, metronidazole, tetracycline (BMT) and a H2RA) consistently achieve eradication rates exceeding 85% and 77%, respectively.[11-19] However, due to the complexity of the bismuth-based quadruple regimen, the PPI-based triple therapy regimen represents the current first-line treatment for patients with *H pylori*. The BMT regimen is often used when cost and/or treatment failure is an issue.[20,21] Although high eradication rates have been observed in Europe with 7 days of treatment,[22-24] clinical trials performed in the United States have found that the highest rates of eradication with either regimen are achieved with higher doses and longer (10 to 14 days) durations of treatment.[25-27]

No randomized studies have compared the various anti-*H pylori* regimens with regard to outcome measures of symptom relief, patient compliance, and tolerance in *H pylori*–positive patients with uninvestigated dyspepsia. Therefore, the aim of this study was to compare the effects of 2 widely used *H pylori* regimens (PPI-based regimen versus BMT regimen) on these outcome measures in patients with uninvestigated ulcer-like dyspepsia and documented *H pylori* infection.

MATERIALS AND METHODS

The institutional review boards of the study sites approved the study protocol prior to study initiation. All subjects provided written informed consent prior to initiation of any study-related procedures.

Study Design and Patient Selection
The study was conducted as a randomized dual center clinical trial. Subjects who were ≥18 years of age and had ≥8-week history of persistent or episodic dyspeptic symptoms (defined as pain or discomfort centered in the upper abdomen of at least moderate severity) and positive *H pylori* results (by serology and urea breath test) were eligible for study enrollment. Subjects were excluded from study participation if their pain/discomfort was suggestive of gastroesophageal reflux disease or irritable bowel syndrome (ie, heartburn, regurgitation, or disturbance of defecation) or if they had evidence of active esophageal, gastric, or duodenal ulcers, erosive esophagitis, gastric malignancy, pyloric obstruction, Barrett's esophagus, esophageal stricture requiring dilatation, or evidence of bleeding by endoscopy. Subjects with a history of gastric or esophageal surgery, prior treatment with an anti-*H pylori* treatment regimen, or the use of a PPI within the prior month, and those who required long-term use of ulcerogenic drugs, including nonsteroidal anti-inflammatory drugs or systemic corticosteroids, or greater than 325 mg/day of aspirin were excluded. The subjects who displayed evidence of current alcohol or drug abuse or were pregnant or lactating were also excluded from study participation.

Medication
Subjects who met the study entry criteria were randomized in a 1:1 ratio to receive 14 days of treatment with either bismuth subsalicylate (Pepto-Bismol, Proctor & Gamble, Cincinnati, OH) 2 tablets, metronidazole 250 mg tablet, tetracycline 500 mg tablet (BMT), each administered 4 times daily (at 8:00 AM, 12:00 PM, 4:00 PM, and 8:00 PM) plus cimetidine 400-mg tablet administered twice daily (at 8:00 AM and 8:00 PM) or lansoprazole 30-mg tablet, amoxicillin 1000-mg tablet, and clarithromycin 500-mg tablet (LAC), each administered twice daily at 8:00 AM and 8:00 PM.

Patient Symptoms
At the pretreatment visit, all patients completed a gastrointestinal symptoms rating scale (GSRS) questionnaire that rated symptoms of stomach ache/pain, heartburn, acid reflux, hunger pains, nausea, stomach rumbling, bloating, burping, flatulence, constipation, diarrhea, stool consistency and urgency on a 7-point scale (where 0 = no discomfort at all and 6 = very severe discomfort). At the pretreatment and the posttreatment (day 15) visits, patients were given a supply of antacid (Gelusil tablets, Parke-Davis, New York, NY) to be taken as needed for the relief of pain and/or discomfort. The amounts of antacid tablets consumed were assessed at the posttreatment (day 15) and final visit (week 8) by tablet count. The GSRS questionnaire was repeated at the final (week 8) visit.

Patient Compliance and Side Effects
To enhance compliance, patients were given a daily diary to record the administration of the study medications. The patients were evaluated for compliance at the posttreatment (day 15) visit by both pill count and questioning by the investigator or study coordinator. All patients were interviewed for possible side effects by the investigator and instructed to contact the investigator if a side effect occurred during therapy. Side effects were graded as mild (transient and easily tolerated by patient), moderate (causes patient discomfort and interrupts usual activities), and severe (causes considerable interference with the patient's usual activities, may be incapacitating, or life-threatening). Side effects were also assessed with regard to the relationship to study drug and graded as probable (strong temporal rela-

Table 1. Gastrointestinal Symptom Rating Scale (GSRS) in *Helicobacter pylori*–Positive Dyspepsia Subjects Before and 8 Weeks after Treatment with BMT and LAC

Study Groups	Before Treatment (Mean GSRS)	After Treatment (Mean GSRS)	*P* value
BMT	1.62	1.13	0.02
LAC	1.67	1.24	0.01
All patients	1.65	1.18	0.0008

BMT = bismuth subsalicylate, metronidazole 250-mg tablet, tetracycline 500-mg tablet plus cimetidine 400-mg tablet
LAC = lansoprazole 30-mg tablet, amoxicillin 1000-mg tablet, and clarithromycin 500-mg tablet

tionship, recurs on rechallenge, and another etiology is unlikely or significantly less likely), possible (strong temporal relationship and an alternative etiology is equally or less likely compared to the potential relationship to the study drug), probably not (an adverse event has little or no temporal relationship to the study drug and/or a more likely alternative exists), and not related (event due to underlying or concurrent illness or effect of another drug and is not related to the study drug).

H pylori Infection and Eradication

Pretreatment serology and the 13C-urea breath test (13C-UBT) was performed according to a standardized protocol, the sensitivity and specificity of which have been reported to be >95%.[28] The bacteriologic response for patients randomized to each treatment regimen was determined by the results of another 13C-UBT performed at the final (week 8) visit and was recorded as positive, negative, or indeterminate if the data were insufficient.

Statistical Analysis

Data were expressed as mean values. Categorical demographic data were analyzed by the Fisher's exact test, Student's *t*-test, or chi-square test. The mean number of antacid tablets taken per study patient were determined and compared between the treatment groups using the Student's *t*-test or the Mann-Whitney rank test. The GSRS results of the 2 treatment groups were compared using the Mann-Whitney rank test, and the pretreatment results were compared with those obtained at the final visit in each treatment group using the Wilcoxon signed rank test. Side effects were summarized by treatment group and compared using Fisher's exact test.

RESULTS

A total of 62 subjects fulfilling the inclusion criteria were enrolled in the study. There were 24 men and 38 women with a mean age of 49.8 years. Sixty subjects completed the 8-week study period and 2 were lost to follow up prior to completion of treatment.

Symptom Relief

At the pretreatment visit, patients randomized to each treatment regimen were similar with respect to reported symptoms and their severity: the mean GSRS for BMT and LAC were 1.62 ± 1.0 and 1.67 ± 1.0 (*P*=NS). At the final (week 8) visit, gastrointestinal symptoms (using the GSRS) improved significantly after treatment with either BMT (1.13, *P*=0.02) or LAC (1.24, *P*=0.01) (Table 1). As assessed by the use of antacid tablets, those treated with LAC experienced greater relief of their dyspepsia symptoms; these individuals consumed significantly fewer antacid tablets compared with those treated with BMT (10.1 tablets versus 27.2 tablets, *P*=0.013).

Table 2. Moderate-to-Severe Adverse Events in *Helicobacter pylori*–Positive Dyspepsia Subjects Treated with BMT and LAC.

Adverse Event	BMT (n=31)	LAC (n=29)
Nausea	4	0
Dizziness/vertigo	1	0
Vomiting	2	0
Diarrhea	3	2
Breast tenderness	1	0
Insomnia	0	1
Bloating	1	1
Rash	1	1
Headache	2	0
Influenza	1	0
Restlessness	1	0
Abdominal pain	0	1
Total no. of events (no. of patients)	17 (12*)	6 (4*)

*P=0.029
BMT = bismuth subsalicylate, metronidazole 250-mg tablet, tetracycline 500-mg tablet plus cimetidine 400-mg tablet
LAC = lansoprazole 30-mg tablet, amoxicillin 1000-mg tablet, and clarithromycin 500-mg tablet

Patient Compliance and Side Effects
Patient compliance was significantly higher with the twice-daily LAC regimen as compared with the 4-time-daily BMT regimen; 92.9% of patients treated with LAC were greater than 90% compliant with the 14-day treatment regimen as compared with 62.1% of those who were randomized to BMT (P=0.006).

The incidence of adverse events was similar in the LAC and BMT groups, 34.5% and 41.9%, respectively (P=0.055); however, a greater incidence of moderate-to-severe adverse events were reported among those treated with BMT compared with LAC (38.7% versus 13.8 %, P=0.029) (Table 2). Moderate-to-severe adverse events probably or possibly related to study medications were observed more frequently among those treated with BMT compared with LAC (35.5% versus 13.8%, P=0.05).

***H pylori* Eradication**
Overall, 86.8% of the patients who were treated with either regimen were cured of *H pylori* infection (Table 3). The eradication rates were 85.7% and 88.0% for BMT and LAC, respectively (P=NS).

DISCUSSION
When patients with uninvestigated dyspepsia, who account for 4% of all office visits, initially present to their primary caregivers, they could have peptic ulcer disease, functional dyspepsia, or gastroesophageal reflux disease.[29] Although general guidelines recommend performing endoscopy in patients with alarm features or who are older, the initial approach for younger uninvestigated patients with dyspepsia is less clear.[30,31] The options in the latter scenario are empiric medical therapy with PPI, "test-and-treat" for *H pylori,* or "test-and-endoscope."

Several decision analysis models and clinical studies have supported the "test-and-treat" approach.[32-34]A randomized trial by Chiba et al also showed significant symptom improvement with eradication of *H pylori* when compared with

Table 3. Comparison of Patient Characteristics and Results of Treatment with BMT and LAC

	BMT (n=31)	LAC (n=29)	*P* value
Mean age	48.1	51.8	NS
Sex (male/female)	14/17	9/20	NS
Medication compliance (%)	62.1	92.9	0.006
Gelusil use (mean no. of tablets)	27.2	10.1	0.013
Moderate-to-severe adverse events (% patients)	38.7	13.8	0.029
H pylori eradication (% patients)	85.7	88	NS

BMT = bismuth subsalicylate, metronidazole 250-mg tablet, tetracycline 500-mg tablet plus cimetidine 400-mg tablet
LAC = lansoprazole 30-mg tablet, amoxicillin 1000-mg tablet, and clarithromycin 500-mg tablet

no therapy in *H pylori*–positive patients with uninvestigated dyspepsia.[35] This "test-and-treat" approach also appears to be cost-effective.[36,37] This approach might also be better than "test-and-endoscope" approach in patients with uninvestigated dyspepsia.[38] It is believed that when the background prevalence of *H pylori* is high, a "test-and-treat" approach may be reasonable for improving symptoms and quality of life in these patients.[36] However, to the authors' knowledge, there has been no randomized trial comparing the outcomes of the various *H pylori*–eradication regimens in patients with uninvestigated dyspepsia.

In this randomized trial, which compared a PPI-based eradication regimen to a low-cost eradication regimen, treatment with either regimen produced a high rate of *H pylori* cure (approximately 87%) and a significant improvement in gastrointestinal symptoms compared with baseline. Despite the similar effect on *H pylori* eradication, symptom improvement (as assessed by antacid consumption) was significantly greater among those treated with the LAC than among those treated with the BMT regimen. Not surprisingly, a significantly higher percentage of patients were able to comply with the less complicated twice-daily LAC regimen compared with those treated with the 4-time-daily BMT treatment course. The LAC regimen was also better tolerated compared with BMT.

The greater benefit from LAC on dyspepsia symptom relief may be related to the antisecretory PPI component of the regimen. In placebo-controlled studies of patients with dyspepsia, statistically significantly greater percentages of patients treated with lansoprazole or omeprazole experienced complete symptom relief following 4 weeks of treatment.[39,40] The more potent antisecretory activity of the lansoprazole component as compared to the H2RA (cimetidine) of the BMT regimen may also explain the difference in symptom response. Jones and colleagues found that a significantly greater proportion of patients with reflux-like or ulcer-like dyspepsia symptoms treated with lansoprazole 30 mg once-daily were symptom-free when compared with patients treated with ranitidine 150 mg twice-daily.[40]

Although *H pylori* infection is susceptible to a variety of treatment regimens that combine an antisecretory agent with at least 2 antimicrobial agents, clinical studies, as well as daily practice, have revealed that there are several issues that deserve consideration when selecting a currently approved treatment regimen for *H pylori*. These include *H pylori* cure rate, rate of regional antimicrobial resistance, and

relative cost of the regimens. In addition, factors that adversely affect patient compliance that may translate into lower eradication rates such as simplicity of administration, daily number of and frequency of medication administrations, effect on gastrointestinal symptoms, tolerability, and side effects should also be considered.

This study compared the effect on patient dyspepsia symptoms, compliance, side effects, and eradication rate in patients treated with the BMT regimen and those treated with the LAC regimen. Although the acquisition cost of the BMT regimen is less than that of LAC regimen, the expenses that result from poor patient compliance and side effects leading to treatment failure, the need to re-treat, and the potential for antimicrobial resistance with BMT may be far greater. One study documented a 25% attrition rate among patients randomized to treatment with BMT regimen.[41] Lerang and colleagues found a significantly higher incidence of side effects in *H pylori*–infected patients who were treated with a bismuth-based regimen versus a PPI-based triple therapy regimen.[42] The increased complexity of the BMT regimen (more tablets administered more frequently) as compared with the PPI-based twice-daily regimen may be an important factor for patient compliance and treatment success.[43]

In conclusion, twice-daily treatment with the triple therapy regimen of LAC is convenient to administer and provides a high rate of *H pylori* eradication in *H pylori*–positive patients with uninvestigated dyspepsia. These patients experience an improvement in their symptoms of dyspepsia and a low rate of side effects when compared with a BMT regimen. These factors likely play a significant role in the high (>90%) rate of patient compliance with the LAC regimen.

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