Treatment of Patients With Persistent Heartburn Symptoms: A Double-Blind, Randomized Trial

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Background & Aims: **Common treatment practices in patients who continue to be symptomatic on proton pump inhibitor once-daily treatment include either increasing the dosage or the use of supplemental medication. This trial's purpose was to compare 2 therapeutic strategies, increasing the proton pump inhibitor dosage to twice daily versus switching to another proton pump inhibitor, in patients with persistent heartburn while receiving standard-dose proton pump inhibitor therapy.** ***Methods:*** **This multicenter, randomized, double-blind, double-dummy trial included patients with persistent heartburn symptoms while receiving therapy with lansoprazole 30 mg once daily. Patients were randomly assigned to treatment for 8 weeks with either single-dose esomeprazole (40 mg once daily) (n = 138) or lansoprazole 30 mg twice daily (n = 144). The primary efficacy variable was the percentage of heartburn-free days from day 8 to the end of treatment.** ***Results:*** **Single-dose esomeprazole was at least as effective as twice-daily lansoprazole for the primary end point of percentage of heartburn-free days during the study period (54.4% and 57.5%, respectively). Symptom scores improved from baseline in similar numbers of patients for heartburn (83.3% of patients in each group), acid regurgitation (76.8% vs 72.9%, $P = .58$), and epigastric pain (67.4% vs 61.1%, $P = .32$), and rescue antacid use was also similar (0.4 tablets/day vs 0.5 tablets/day, $P = .50$).** ***Conclusions:*** **Switching patients with persistent heartburn on a standard-dose proton pump inhibitor to a different proton pump inhibitor was as effective as increasing the proton pump inhibitor dosage to twice daily for controlling heartburn symptoms.**

Gastroesophageal reflux disease (GERD) is recognized as a common, persistent medical problem, of which the primary symptom is heartburn. Approximately 40% of the adult population reports heartburn at least once a month, and 7% report daily heartburn.[1–3] Acid-suppressive therapy decreases the amount of acid exposure in the distal esophagus and provides healing of esophageal mucosal injury and relief from a variety of GERD-related symptoms. Presently, proton pump inhibitors (PPIs) have become the standard treatment for these symptoms because of their unsurpassed ability to provide prolonged acid suppression, which results in high healing and symptom resolution rates. Failure of PPIs to completely resolve symptoms has become a commonly encountered clinical dilemma in gastroenterology practices. In one study, approximately 25% of the patients with uninvestigated GERD continued to have heartburn symptoms despite treatment with standard-dose PPI once daily.[4]

The doses of esomeprazole and lansoprazole approved by the Food and Drug Administration for treatment of symptomatic GERD are 20 mg and 15 mg, respectively.[5,6] However, in our opinion, it is common clinical practice to initiate therapy with esomeprazole 40 mg once daily or lansoprazole 30 mg once daily. Our current standard of practice in patients who failed PPI once-daily therapy is to double the PPI daily dosage or to add a supplemental medication.[7] Therefore, the aim of this trial was to compare the efficacy and safety of 2 potential therapeutic strategies, esomeprazole 40 mg once daily versus increasing the lansoprazole dosage to 30 mg twice daily, in patients who continued to have persistent heartburn symptoms while receiving lansoprazole 30 mg once daily. The hypothesis tested was that switching to esomeprazole 40 mg once daily is at least as clinically effective as lansoprazole 30 mg twice daily for the relief of heartburn symptoms.

Materials and Methods

Study Design

This multicenter, randomized, double-blind, double-dummy, parallel-group trial (D9612L0005/Study 311) was conducted in the United States, was performed in accordance

Abbreviations used in this paper: AE, adverse event; CI, confidence interval; GCP, good clinical practice; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; SEM, standard error of the mean.

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with the principles of the Declaration of Helsinki, and was consistent with good clinical practice regulations issued by the US Food and Drug Administration. The institutional review boards at each site approved the protocol, and all patients provided written informed consent before enrollment.

This 10-week clinical trial consisted of a 2-week baseline symptom-assessment period, during which patients continued taking lansoprazole 30 mg once daily, and an 8-week treatment period, during which patients were randomly assigned to treatments with esomeprazole 40 mg once daily and lansoprazole 30 mg twice daily. Patients were randomized to the 2 treatment arms by using blinded blocks of 4 allocation numbers at each center (concealed allocation to treatment in a 1:1 ratio). The randomization schedule was computer-generated by the study sponsor. All patients were assigned allocation numbers in sequential order, and allocation numbers were not reassigned if a patient withdrew. Study drug was shipped to centers in multiple blocks. Patients were instructed to take the study medication (active medication or placebo) 30 minutes before breakfast and 30 minutes before dinner. Double-dummy dosing was used to preserve blinding because the 2 medications differ in appearance. Treatment codes including the treatment randomization were to be broken by the investigators only in the event of medical emergencies. Antacid tablets (Gelusil; Warner-Lambert Consumer Healthcare [Parke-Davis], Morris Plains, NJ) were provided as rescue medication for the relief of heartburn symptoms, and patients were permitted to take a maximum of 6 tablets per day. Compliance and rescue medication usage were measured by counting unused capsules and tablets at each study visit.

Patients

Adult patients (age ≥18 years) with a history of heartburn symptoms of any severity for ≥2 days per week during the 30 days before screening while taking lansoprazole 30 mg once daily were eligible for enrollment in the trial. Patients completed a daily symptom diary during the baseline, pre-randomization, screening period of 14–17 consecutive days. Symptom severity during the previous 24 hours was scored as none (0), mild (1; symptoms easily tolerated and not lasting long), moderate (2; symptoms that caused some discomfort but did not interfere with usual activities), or severe (3; symptoms that caused much discomfort and interfered with usual activities). To be eligible for randomization to study treatment, patients must not have missed more than 3 days of recording and must have had a minimum cumulative heartburn score of ≥4 for the duration of the baseline period.

Exclusion criteria included current or historical evidence of esophageal ulcers or strictures, gastric or duodenal ulcers or any other gastric or esophageal pathology judged to be clinically significant by the investigator, significant gastric or esophageal pathology, persistent heartburn symptoms for more than 1 year while receiving lansoprazole, and serologic evidence of *Helicobacter pylori* infection. Also excluded were patients who received any of the following drugs within 2 weeks before the first dose of study drug or needed these drugs for continuous concurrent therapy: theophylline, bismuth salts, warfarin, phenytoin, barbiturates, antineoplastic agents, erythromycin, clarithromycin, or sucralfate. Concomitant medications that rely on the presence of gastric acid for optimal absorption were not permitted during the trial. Women were required to be nonpregnant, nonlactating, and using a medically acceptable form of birth control.

Efficacy Assessments

Patients were instructed to record the severity (by using the 4-point scale as described above) of the symptoms of heartburn, acid regurgitation, and epigastric pain during the previous 24 hours in a symptom diary each morning before taking study medication. Patients also recorded whether nighttime heartburn had been "present" or "absent." Heartburn was defined as a burning feeling rising from the stomach or lower part of the chest toward the neck. Epigastric pain was the perception of discomfort located in the central upper portion of the abdomen. Nighttime heartburn was defined as heartburn that occurred during the night after the patient had assumed the supine sleeping position. Diary cards were collected after 4 and 8 weeks of study treatment. Days 1–7 of the treatment period were considered a washout period for the previous treatment with lansoprazole 30 mg once daily, and symptoms occurring during this period were not analyzed.

The primary clinical outcome was the percentage of heartburn-free days from day 8 to the end of study treatment. Secondary clinical outcomes included percentages of symptom-free days for nighttime heartburn, epigastric pain, and acid regurgitation; weekly average symptom scores; and percentages of patients with symptom improvement from baseline on the basis of weekly symptom scores (mean weekly score during the 2-week baseline period). Symptom improvement was defined as any decrease in weekly symptom scores from baseline. Supplemental antacid usage in each group from day 8 to the end of treatment was also assessed. Also, at the randomization visit and after 4 and 8 weeks, the investigator asked each patient to rate average heartburn symptom severity during the preceding 4 weeks on a 4-point scale.

Tolerability and Safety Assessments

Documentation of medical history, physical examination, and clinical laboratory results was completed at baseline and at the final visit for each patient. Adverse events (AEs) were recorded on the basis of observations or patient responses, either volunteered or given to open-ended questions.

Statistical Analysis

The statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). The analyses included all patients randomized to treatment who took at least 1 dose of study medication, had diary data after day 8, and were from sites that followed good clinical practice guidelines (modified intention-to-treat). The safety population included all patients who took at least 1 dose of study medication and provided safety data after the screening period.