Efficacy and safety of omeprazole in Japanese patients with nonerosive reflux disease

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Background. There is increasing awareness of non-erosive reflux disease (NERD) as a disease requiring treatment in Japan. This randomized, double-blind, placebo-controlled, parallel-group study was conducted to investigate the efficacy and safety of omeprazole 10 mg and 20 mg once daily in Japanese patients with NERD.

Methods. Patients with heartburn for at least 2 days a week during the month before entry into the study and no endoscopic signs of a mucosal break (grade M or N according to Hoshihara’s modification of the Los Angeles classification) were randomly assigned to one of three groups (omeprazole 10 mg, n = 96; omeprazole 20 mg, n = 93; placebo, n = 95). The rate of complete resolution of heartburn in week 4 was significantly higher in patients treated with omeprazole 10 mg [32.3%, 95% confidence interval (CI), 22.9%–41.6%] or 20 mg (25.8%, 95% CI, 16.9%–34.7%) than in the placebo group (12.0%, 95% CI, 5.3%–18.6%). No significant difference between the two omeprazole groups was observed. The rate of complete resolution of heartburn by omeprazole was similar between patients with grade M and those with grade N esophagus. Omeprazole also increased the rate of sufficient relief from heartburn. Omeprazole was well tolerated.

Conclusions. Omeprazole 10 mg or 20 mg once daily is effective and well tolerated in patients with NERD regardless of their endoscopic classification.

Key words: nonerosive reflux disease (NERD), heartburn, omeprazole

Introduction

The prevalence of gastroesophageal reflux disease (GERD) in Japanese subjects is approximately 6.6%.1 The major symptom of GERD is heartburn, which is caused primarily by the reflux of acidic gastric contents into the esophagus. GERD is classified into erosive esophagitis and nonerosive reflux disease (NERD) on the basis of endoscopic findings. NERD is a symptomatic disease with no mucosal break in the esophagus according to the Los Angeles (LA) classification. In Japan, NERD is further subdivided into grade M (minimal change in endoscopic findings) or grade N (endoscopically normal mucosa) based on the appearance of the esophageal mucosa, in accordance with Hoshihara’s modified version of the LA classification.2

Recently, the increasing prevalence of NERD3-4 and awareness of its impact on the quality of life5-6 have led to growing acceptance of NERD as a disease requiring treatment in Japan.

Proton pump inhibitors (PPIs) such as omeprazole are the most effective agents currently available for the treatment of NERD in Western countries.7 Controlled
studies in Europe, North America, and Australia have consistently shown that PPIs produce significantly greater relief of NERD symptoms than H₂-receptor antagonists (H₂RAs) in Caucasian patients. However, few reports are available for Japanese patients. Moreover, the response to the treatment in relation to the endoscopic classification of NERD is unknown.

In clinical practice, it is not feasible to perform 24-h intrasophageal pH monitoring or a PPI test on every patient with heartburn to determine whether the symptoms are acid-related. Another practical tool for identifying responders to PPIs is their efficacy during early treatment.

In this paper, we present results from a randomized, double-blind, placebo-controlled, parallel-group study on the efficacy and safety of omeprazole 10 mg or 20 mg once daily in Japanese patients with NERD. Efficacy in patients with grade M or N NERD was also investigated in the study.

Methods

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 33 centers in Japan. The study was conducted in compliance with good clinical practice, and the study protocol was approved by the institutional review board at each study center. Written informed consent to participate in the study was obtained from every patient before study entry.

Subjects

The inclusion criteria of the study were (1) provision of written informed consent, (2) female or male, aged 20 years or more, (3) patients who identified their predominant symptom as heartburn, (4) patients with a history of moderate or severe heartburn episodes for 2 days or more each week for at least a month just before the screening, and (5) patients who were classified as having a grade M or N esophagus according to Hoshihara's modified version of the LA classification by endoscopy at the screening. Patients with erosive esophagitis or those with a history of this condition were excluded from the study.

Study design and procedures

At the initial visit, patient eligibility and the severity of heartburn were determined, and endoscopy was performed to classify the esophagus according to Hoshihara's modified version of the LA classification by endoscopy at the screening. Patients with a hiatal hernia were excluded from the study.

Efficacy assessments

The primary objective of the study was to compare the efficacy of omeprazole 10 mg or 20 mg to placebo in patients with NERD in terms of the complete resolution of heartburn (defined as no heartburn for 7 consecutive days) during the fourth week of treatment. Secondary efficacy variables were the rate of sufficient relief from heartburn (defined as no heartburn or no more than 1 day with mild heartburn for 7 consecutive days) during the fourth week of treatment.

Heartburn was recorded by patients on diary cards. Heartburn was defined as a burning feeling, rising from the stomach or lower part of the chest toward the neck. The severity of heartburn was assessed on a four-point scale: none (no heartburn), mild (awareness of heartburn but easily tolerated), moderate (discomforting heartburn sufficient to cause interference with daily activities), or severe (incapacitating heartburn, causing inability to perform daily activities).

Safety assessments

Safety was assessed by monitoring adverse events throughout the study period and by clinical laboratory tests (clinical chemistry, hematology, and urinalysis) at the start and end of the study.

Genotyping of CYP2C19

Samples for genetic analysis were collected during the study period. The CYP2C19*2 allele was identified by polymerase chain reaction (PCR)-based allele-specific amplification of exon 5 of CYP2C19 followed by digestion with the restriction enzyme Smal. Similarly the CYP2C19*3 allele was analyzed by PCR amplification of exon 4 of CYP2C19 followed by digestion with the restriction enzyme BanHII. On the basis of the results of these assays, patients were classified as being a homozygous extensive metabolizer (EM), a heterozygous...