Study Design

Patients

The open-labeled trial is conducted at the Kaohsiung Veterans General Hospital, Kaohsiung Medical University Hopsital and Kaohsiung Chang Gung Memorial Hospital in Taiwan in accordance with the principles of good clinical practice from the Declaration of Helsinki. The study protocol was approved by the Ethics Committees in each study center. All patients will be given written informed consent before participating in the study. Patients between the ages of 20 and 80 years with clinical symptoms of acid regurgitation, heart burn, or feeling of acidity in the stomach, who have Barrett's Esophagus proven by histology confirmation of esophageal metaplastic mucosa with length equal to or longer than 1 centimeter will be enrolled. Criteria for exclusions include (1) pregnancy, (2) coexistence of serious concomitant illness (for example, decompensated liver cirrhosis and uremia), (3) previous gastric surgery, (4) allergy to esomeprazole, (5) presence of dysplastic esophageal mucosa, and (6) equivocal endoscopic diagnosis of Barrett's esophagus (e.g., esophageal metaplastic mucosa less than 1 cm).

Study Design and Randomization

Eligible patients will be randomly assigned to receive either (1) on-demand PPI

therapy (40 mg of esomeprazole [Nexium, AstraZeneca, Sodertalje, Sweden] daily for 8 weeks, and then on-demand esomeprazole 40 mg daily if symptoms recurred.) or (2) continuous PPI therapy (40 mg of esomeprazole daily for 48 weeks). Randomization will be carried out with the use of a computer-generated list of random numbers. An independent staff member assigns the treatments according to consecutive numbers that are kept in sealed envelopes. The participants in the on-demand group will be instructed to take esomeprazole 40 mg daily for consecutive three days whenever reflux symptoms bothered them. If patients have obvious reflux symptoms soon after discontinuing PPI therapy twice or more, on-demand PPI treatment could be switched to continuous PPI use. In the continuous PPI therapy group, the participants take esomeprazole 40 mg daily no matter symptoms develop or not. All the participants are instructed to take esomeprazole 30 minutes before breakfast.

They are requested to complete a Chinese GERDQ on enrollment. The total score of GERD symptoms will be recorded. Each participant should complete diary cards during the study period. They return to the clinics for drug refills and evaluation of reflux symptoms every month. The participants are asked to hand in daily symptom records at each visit, and to report the number of esomeprazole tablets taken per 4-week period. Follow-up endoscopy with biopsy for esophageal mucosal metaplasia

will be performed at the end of 48 weeks.

Endoscopy

Endoscopy is performed on enrollment, and the esophagus is carefully evaluated. Endoscopic suspected esophageal metaplasia (ESEM) is defined as a tongue-shaped projection of salmon-colored mucosa from the esophagogastric junction (the point where the proximal end of the gastric folds meets the tubular esophagus). All of the four quadrants of ESEM will be sampled every 2 cm. The Barrett's esophagus is defined as gastric or intestinal metaplastic change of distal esophageal epithelium confirmed by biopsy. The grade of Barrett's esophagus is scored according to the Prague C & M criteria. All subjects with biopsy-proven Barrett's esophagus will be further categorized into long-segment Barrett's esophagus and short-segment Barrett's esophagus. Long-segment Barrett's esophagus is defined as the maximal length of metaplastic columnar epithelium over distal esophagus equal to or more than 3 cm, and short-segment Barrett's esophagus is defined as the extension of columnar epithelium over distal esophagus less than 3 cm. Erosive esophagitis will be scored using the Los Angeles classification system. Hiatus hernia is defined as a distance between the esophagogastric junction and the diaphragmatic hiatus equal to or more than 1 cm.

H pylori examination

Two biopsy specimens are taken from the lesser curvature sites of the antrum, and another two from the corpus. They will be fixed in 10% buffered formalin, embedded in paraffin, and sectioned. The sections, 4-μm thick, will be stained with a haematoxylin and eosin stain and a modified Giemsa stain to observe the presence of curved rod shape bacteria on the mucosal surface. Biopsy specimens will be assessed by histopathologists, who are blinded to patient status and the results of other laboratory tests.

Questionnaire

A standardized data-collection form for medical history and demographic data will be obtained from each patient on enrollment, including age, sex, body mass index (BMI), medical histories, histories of smoking, alcohol, coffee and tea consumption. Smoking is defined as consumption of cigarettes 1 pack or more per week. Coffee or tea consumption is defined as drinking 1 cup or more per day.

Chinese GERDQ is a validated symptom questionnaire for the diagnosis and severity evaluation of gsatroesophageal reflux disease. In the scoring system, the evaluated symptoms include acid regurgitation, heartburn and feeling of acidity in the stomach. The severity of symptoms in the questionnaire are graded on a five-point

Likert scale as follows: 1 (none; no symptoms); 2 (mild: symptoms can be easily ignored); 3 (moderate: awareness of symptoms but easily tolerated); 4 (severe: symptoms sufficient to cause an interference with normal activities); 5 (incapacitating: incapacitating symptoms with an inability to perform daily activities or work), and frequency of symptoms are graded as follows: 1 (none in the past year); 2 (less than once per month); 3 (≥ once per month); 4 (≥ once per week); 5 (≥ once daily). A cut-off score of ≥12 is used to make the diagnosis of symptomatic GERD.

***Genotyping of* CYP2C19**

Blood sampling for genotyping of CYP2C19 will be carried out after endoscopy for the subjects who provides informed consent for genetic study. The *CYP2C19* genotype is determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Genotypes are classified into three groups: homEM (*CYP2C19**1/*CYP2C19**1); hetEM (*CYP2C19**1/*CYP2C19**2 and *CYP2C19**1/*CYP2C19**3); PM (*CYP2C19**2/*CYP2C19**2, *CYP2C19**2/*CYP2C19**3, and *CYP2C19**3/*CYP2C19**3).

End Points

The primary outcome measures are (1) histological progression of metaplastic

esophageal epithelium at 48 weeks, and (2) total symptom days within the 48-week study period. The secondary outcome measure is total PPI consumption during the 48-week study period. Histological progression of metaplastic esophageal epithelium is defined as (1) progression from gastric metaplasia into intestinal metaplasia, low grade-dysplasia or high-grade dysplasia, or (2) progression from intestinal metaplasia into low-grade or high-grade dysplasia.

Statistics

Our study is designed as a non-inferiority trial. Sample size was calculated from numbers needed to show that on-demand therapy is non-inferior to continuous therapy based on the proportion of patients who would discontinue the study prematurely because of unsatisfactory therapy. The hypothesis for sample size calculations are based on 94% on-demand therapy continuation rate and 92% continuous therapy continuation rate. On-demand therapy is defined as non-inferior to continuous therapy if the upper bound of the two-sided 90 % CI for the difference in proportions (on-demand minus continuous) is less than 10 %.

With a sample size of 78 patients in each treatment group, a one-sided test of proportions at the 5 % level had 90 % power to reject the hypothesis that on-demand therapy is inferior to continuous treatment. With an assumption of 10 % non-evaluable

patients and 10% non-eligible patients for randomization, it was calculated that 196 patients would be required in the initial enrollment to yield sufficient power.

Statistical analysis will be performed using the Statistical Program for Social Sciences (SPSS 19.0 for windows). Univariate analysis is performed by Student's t test for continuous variables and χ^2 test is used for categorical variables. $P < 0.05$ is considered statistically significant and all reported p values are two-sided.