ORIGINAL ARTICLE

An open-label, non-comparative, non-interventional, multi-center, post-authorization safety study on the administration of rabeprazole to adults with gastro-esophageal reflux disease

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Abstract

Background Rabeprazole produces a profound and long-lasting inhibition of gastric acid secretion. The aim of the study was to monitor the safety and efficacy of rabeprazole administered to patients with erosive or symptomatic non-erosive reflux disease, in real-life healthcare settings.

Methods Male and female patients, aged ≥18 years, with endoscopy diagnosed GERD were included; patients received at least 8 weeks treatment with rabeprazole. Changes in severity of symptoms recorded on the Likert scale were analysed using marginal homogeneity tests.

Results 186 patients were enrolled across 17 study sites; 127 patients (68.3%) completed the study. Almost 75% of patients had an initial diagnosis of GERD with Grade A or B esophagitis. The most commonly reported adverse events (AEs) were diarrhea, flatulence, dizziness, cough, abdominal pain, upper abdominal pain and somnolence. Over half of AEs were unrelated to study drug; 1 severe AE of diarrhea was possibly related to study drug. No new AEs were reported not included in the current version of Summary of Product Characteristics. Rabeprazole was effective in reducing the symptoms of GERD; the Likert scale scores of symptoms decreased significantly for all patients from 0-4 weeks and 4-8 weeks.

Conclusions In our study, rabeprazole was safe and effective in reducing the symptoms of GERD.

Keywords Rabeprazole, post-authorization safety study, gastro-esophageal reflux disease, real-life clinical practice

Ann Gastroenterol 2014; 27 (2): 133-138

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Introduction

Rabeprazole sodium belongs to the substituted benzimidazole group of anti-secretory agents that inhibit gastric acid secretion by the specific inhibition of the H^+/K^+-ATPase enzyme (proton pump) of gastric parietal cells; rabeprazole produces a profound and long-lasting inhibition of gastric acid secretion [1,2].

Rabeprazole is indicated for the treatment of active duodenal ulcer, active benign gastric ulcer, symptomatic erosive reflux disease (ERD), gastro-esophageal reflux disease (GERD) long-term management (GERD maintenance treatment), symptomatic treatment of moderate to very severe non-erosive ERD (NERD), Zollinger-Ellison syndrome, and in combination with appropriate antibacterial therapeutic regimens for

the eradication of *Helicobacter pylori (H. pylori)* in patients with peptic ulcer disease [3].

This post-authorization safety study (PASS) was undertaken in accordance with European and International Pharmacovigilance Guidelines, which require that the safety and efficacy of drugs should be continuously monitored even after receiving marketing approval. The objective of the study was to collect data regarding the safety and efficacy of rabeprazole administered to adult patients with ERD or with symptomatic GERD, in the real-life clinical practice. The effectiveness of rabeprazole was assessed with endoscopy assessments and by monitoring symptoms.

Patients and methods

Study design, population, and treatments

This was an open-label, non-comparative, multi-center study undertaken in primary healthcare settings in Greece between 12 March 2003 and 25 November 2005. The study design followed the applicable requirements of the European guidelines on clinical studies (2001/20/EC) and specifically on non-interventional studies, as well as the applicable requirements of the European pharmacovigilance guidelines CPMP/PhVWP/108/99 regarding observational safety studies. All patients gave written informed consent.

The study included male and female patients aged ≥18 years with endoscopy diagnosed ERD or NERD and with no Barrett type metaplasia. Patients should have experienced symptoms of their disease for at least 3 months before entering the study, including experiencing symptoms for at least 3 days per week within the 2 weeks before entering the study; symptoms could include heartburn, retrosternal pain and regurgitation. A patient could only be considered for participation in the study after a gastroenterologist had diagnosed GERD and prescribed treatment with rabeprazole. Upper endoscopic evaluation was, also, required for documenting the presence or absence of esophagitis. Patients were excluded for any of the following reasons: any type of esophageal narrowing or esophagitis of secondary systemic causes; active gastro-duodenal ulcer; infections other than *H. pylori* gastritis; inflammatory conditions of small or large intestine; malabsorption syndromes; previous surgeries in stomach or intestine, including vagotomy (patients with history of ulcer, appendectomy or cholecystectomy could participate in the study); a recorded history of primary kinetic disorders of esophagus other than GERD, or esophageal or stomach varices; treatment with proton pump inhibitors within the 2 weeks before entering the study; co-existing severe systemic disease, including renal, hepatic and heart failure; receiving cancer treatment within the previous year (patients with successfully treated superficial basal cell carcinoma were allowed to participate); Zollinger-Ellison syndrome; endoscopic evidence of active, hemodynamically significant, gastro-esophageal hemorrhage; frequent use of aspirin, except in cases of prophylactic cardiovascular use at doses lower than 300 mg daily, or daily use of non-steroid anti-inflammatory drugs.

The study comprised 4 clinic visits at week 0, week 4, week 8 and month 4 (visits 1-4) and telephone contact at 6 and 12 months (visits 5 and 6). Patients were monitored for 12 months thereafter.

Patients received rabeprazole treatment for 8 weeks starting with a single 20 mg tablet before breakfast. The dose could be adjusted according to investigators assessment for the management of patients' disease. Dosing could continue after the 8-week study treatment period. During the study, drugs that are absorbed in a gastric pH dependent manner, such as ketoconazole, esters of ampicillin and iron salts were not allowed.

Safety assessments

Adverse events (AEs) were monitored from completion of 4 weeks of treatment until the end of the study. Clinical and physical examinations (including vital signs) and laboratory analyses were undertaken throughout the trial.

Effectiveness assessments

The degree of esophagitis was determined by endoscopy according to the Los Angeles classification [4].

The symptoms of ERD and the relationship between severity and the degree of esophagitis were recorded before entering the study, on the first day of treatment and after 7 days of treatment; patients were interviewed using telephone questionnaires on days 1 and 7.

Symptom severity was further assessed at 4 weeks, 8 weeks, 4 months, 6 months and 12 months after the start of treatment. Recurrence was evaluated at 4, 6 and 12 months after the start of treatment.

Endoscopy assessments were undertaken at 8 weeks and 4 months after the start of treatment, if required according to the clinical practice of the study center.

Severity of symptoms and recurrence

Severity was determined for the symptoms of heartburn, retrosternal pain and regurgitation using the 5-point Likert Scale: 1, no problem; 2, mild problem, can be ignored with effort; 3, moderately severe problem, cannot be ignored but does not influences daily activities; 4, severe problem, cannot be ignored and often limits my concentration on daily activities; 5, very severe problem, cannot be ignored and markedly limits my daily activities and often requires rest [5].

Recurrence was defined as at least 2 weekly episodes of heartburn of at least severity 3 after improvement in symptoms (heartburn severity ≤2) had been achieved during the previous treatment period.

Statistical methods

It was planned to recruit 300 patients in the study. This

allowed for up to 15 patients to be recruited at each of the 17-21 potential study sites. The intent-to-treat (ITT) population included all patients enrolled in the study; this population was used for all the analyses. All patients included in the ITT population received at least 1 dose of rabeprazole. One patient was enrolled but did not provide any data so was excluded from the analysis.

All data were summarized descriptively. To test if there was a correlation between the different baseline characteristics, t tests were used. Categorical values were compared using a chi-square test [6]. Logistic regression analysis was performed to determine the effects of factors or covariates on binary variables [6]. McNemar tests were used to determine if 2 probabilities of success were equal at 2 time points or experimental conditions [6].

AEs were classified according to MedDRA version 13.0. A correlation between incidence of AEs and demographic data, clinical characteristics and concomitant medications was undertaken using a logistic regression model. Missing observational data for drug safety were not replaced. Concomitant medications were coded using the World Health Organization Drug Dictionary (WHODRUG) Q1 2008 and Anatomical-Therapeutic-Chemical (ATC) codes.

Marginal homogeneity tests were used to determine the equality of Likert scale scores between successive visits [6,7]. All testing was 2-sided at α=5% significance level; statistically significant differences were indicated by P values <0.05. Missing data for effectiveness variables were not replaced.

All analyses were performed using SAS version 8.02 (SAS Institute, Cary, NC USA).

Results

Participants

A total of 186 patients were enrolled across the 17 study sites and were included in the ITT analysis. 127 patients (68.3%) completed the 12 month study period. 59 patients withdrew; no data were obtained from one patient, 35 patients were lost to follow up and 11 patients withdrew their consent (Fig. 1). Withdrawals most commonly occurred during the 8-week treatment period, but there was another peak in the last 6 months of the study.

Patient demographics are summarized in Table 1. There were approximately equal numbers of male and female patients and their median age (minimum-maximum) age was 55.0 (17-83) years. The most frequently reported types of gastrointestinal history were reflux esophagitis, gastritis, NERD and previous eradication of *H. pylori*. Almost 75% of patients had an initial diagnosis of GERD with Grade A (77 patients) or Grade B (60 patients) esophagitis. Age and gender, age and smoking, age and alcohol consumption, smoking and gender, smoking and alcohol consumption and alcohol consumption and gender were all confounding factors (data not shown).
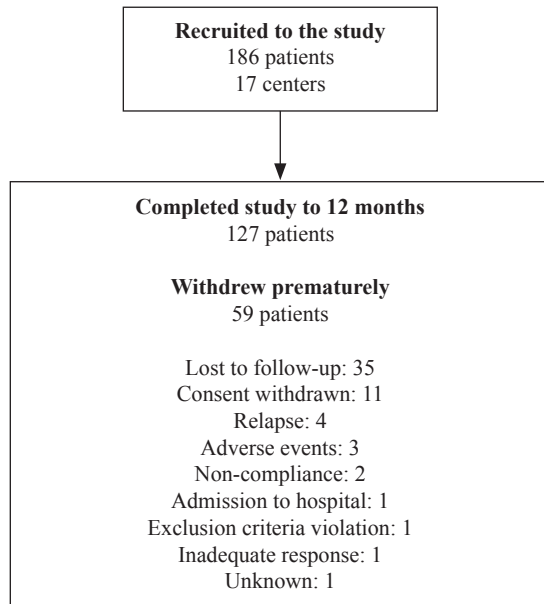
There was a statistically significant relationship between

initial diagnosis and withdrawal from the study (χ213.941; P=0.003); more patients with an initial diagnosis of NERD or GERD with esophagitis Grade C or D withdrew from the study. There was no statistically significant relationship between withdrawals and age, gender, smoking status or alcohol consumption. Seven patients were lost to follow-up and were

Table 1 Patient demographics

Variable	
Age, years	
N	180
Mean (SD)	52.2 (16.6)
Median (minimum-maximum)	55.0 (17-83)
Gender, n (%)	
N	185
Male	92 (49.7)
Female	93 (50.3)
Weight, kg	
N	177
Mean (SD)	78.4 (16.5)
Smoking, n (%)	
N	185
Smoker	48 (25.9)
Non-smoker	137 (74.1)
Alcohol consumption, n (%)	
N	185
Yes	52 (28.1)
No	133 (71.9)
NSAID consumption, n (%)	
N	185
Yes	23 (12.4)
No	162 (87.6)
Medical history, n (%)	
N	185
History in at least one system	116 (62.7)
No medical history	69 (37.3)
Gastrointestinal history, n	
N	185
Reflux esophagitis	54
Gastritis	50
GERD without esophagitis	45
Previous eradication of *H. pylori*	30
Duodenal ulcer	9
Benign gastric ulcer	1
Initial diagnosis, n (%)	
N	185
GERD with Grade A esophagitis	77 (42.3)
GERD with Grade B esophagitis	60 (32.4)
GERD with Grade C esophagitis	22 (11.9)
Symptomatic GERD without esophagitis	21 (11.5)
GERD with Grade D esophagitis	2 (1.1)

¹*One patient had an extreme weight value (216 kg)*
N, total number of patients in data set; SD, standard deviation; n, number of patients; NSAID, non-steroid anti-inflammatory drug; GERD, gastro-esophageal reflux disease

Recruited to the study
186 patients
17 centers

↓

Completed study to 12 months
127 patients

Withdrew prematurely
59 patients

Lost to follow-up: 35
Consent withdrawn: 11
Relapse: 4
Adverse events: 3
Non-compliance: 2
Admission to hospital: 1
Exclusion criteria violation: 1
Inadequate response: 1
Unknown: 1

Figure 1 Patient flow chart

withdrawn from the study by the investigators after visit 2; these patients were included in the ITT population, and their inclusion did not change the results of the analysis of the relationship between withdrawals and patient demographics.

As this was a non-interventional study, the length of the treatment period was at the discretion of the physician, whilst the observation period was for 1 year.

Safety and tolerability

During the study, 49 patients reported at least 1 AE (26.3%). The AEs most commonly reported (reported by ≥5% of patients) were diarrhea, flatulence, dizziness, cough, abdominal pain, upper abdominal pain and somnolence. Most AEs were mild (57.4%) or moderate (39.4%). More than half of AEs were unrelated to study drug. One severe case of diarrhea was considered to be possibly related to study drug and two AEs (dry mouth and tinnitus) were considered to be at least possibly associated with study drug. Most AEs required no intervention and the majority had resolved by the end of the study. One patient suffered a myocardial infarction, which was considered to be unrelated to the study drug.

There were no clinically significant out of range laboratory results or vital signs during the study period.

Concomitant medications were taken by 89/185 (48.1%) patients during the study. AEs were reported by 34/89 (38.2%) patients receiving concomitant therapy compared with 15/96 (15.6%) patients with no concomitant therapy ($\chi2$=12.090, P=0.001).

Effectiveness results

The number of patients reporting no or mild symptoms

on the Likert scale increased throughout the study. For all patients, marginal homogeneity tests showed that the decrease of symptoms from the start of the study to the end of 4 weeks was statistically significant, as was the decrease of symptoms from the end of 4 weeks to the end of 8 weeks. For the subgroup of patients with NERD, the decrease of symptoms from the start of the study to the end of 4 weeks was statistically significant.

Information about remission (the decrease of severity or frequency of GERD symptoms) was recorded for 171 patients. At the end of 4 and 8 weeks of treatment, 161/171 (94.2%) and 151/155 (97.4%) patients, respectively, showed remission of symptoms. After 4 weeks of treatment, remission was recorded in 114/123 (92.7%) patients receiving rabeprazole 20 mg/day and all patients receiving other doses (N=168). After 8 weeks of treatment, 114/116 (98.3%) patients on rabeprazole 20 mg/day and all but one patients receiving other doses reported remission. For the subgroup of patients with NERD who received rabeprazole 20 mg/day, remission was reported by 16/20 (80%) and 10/11 (90.9%) patients after 4 and 8 weeks of treatment, respectively. After 4-month treatment, relapse of symptoms was observed in only 5/136 (3.7%) of all patients and one in the sub-group of patients with NERD.

Discussion

This open-label, non-comparative, multi-center PASS collected data regarding the safety and efficacy of rabeprazole administered to adult patients with ERD or NERD, in the real-life healthcare setting. A patient could only be enrolled in the study after a gastroenterologist had diagnosed GERD and prescribed treatment with rabeprazole and the patient had undergone upper endoscopy.

The study planned to enrol 300 patients across up to 21 study sites, but at last 186 patients were recruited across 17 study sites during the 12-month recruitment period. Considering the nature of the study (open-label, non-comparative, non-interventional) the sample size was acceptable for the main purpose of the study, which was the monitoring of rabeprazole safety.

Almost 75% of patients had an initial diagnosis of GERD with esophagitis Grade A or Grade B. Patients with an initial diagnosis of NERD or ERD with esophagitis Grade C or D were less likely to complete the one year observation period. This was not related to effectiveness however, as many patients with NERD were prematurely withdrawn from the study despite a large improvement in symptoms, possibly because continuous treatment with rabeprazole was not necessary. As this was a non-interventional study, the physician was free to decide the adequate treatment period. However, this was a rather small group of patients so firm conclusions cannot be drawn.

The majority of AEs reported during the study were mild or moderate, and more than half were unrelated to study drug. The most commonly reported AEs of diarrhea, flatulence, dizziness, abdominal pain and upper abdominal pain are all known side effects of rabeprazole; other AEs commonly

associated with treatment with rabeprazole are headache, asthenia (fatigue), rash and dry mouth [4].

Rabeprazole was effective in reducing the symptoms of GERD during the study; there was a significant decrease in the Likert scale scores of symptoms for all patients from 0-4 weeks and 4-8 weeks, and for patients with non-erosive GERD from 0-4 weeks. Remission (decrease in the severity or frequency of symptoms of GERD) was observed in 94.2% patients and 97.4% patients after 4 weeks and 8 weeks, respectively. Only 3.7% patients reported relapse of symptoms after 4 months. The frequency and severity of heartburn symptoms were reduced during treatment with rabeprazole; 60.1% and 70.7% patients had no symptoms of heartburn 24 h and 7 days after the first dose of rabeprazole, respectively, and more than 80% of patients reported their symptoms to be less important 7 days after starting treatment compared with 24 h after starting treatment. Consistent with the reduction in the frequency and severity of heartburn symptoms, the effect of heartburn on daily activities also decreased during the study.

The effectiveness results of our study are comparable with the results of a community-based, open-label assessment of patients with erosive disease that included 2,579 patients with ERD who were treated with rabeprazole 20 mg/day for 8 weeks [8]; complete relief of daytime and night-time heartburn was achieved in 64.0% and 69.2% of symptomatic patients, respectively, on day 1, and in 81.1% and 85.7% of patients, respectively, on day 7. The severity of symptoms of heartburn progressively decreased from day 1 to week 4 of treatment. The severity of symptoms of regurgitation, dysphagia and belching also decreased by day 1 and continued to improve from day 1 to week 4 of treatment. Health-related quality of life scores were significantly improved after 8 weeks of treatment with rabeprazole.

Although patients experienced improvements in their symptoms of GERD during our study, there was no control group and therefore conclusions about the effectiveness of rabeprazole should be made with caution. The sample size of the sub-group of patients with NERD was small, so these results should be interpreted cautiously. Similarly, the sample size included in the analyses of heartburn symptoms was low.

This study has several limitations. First and foremost, although initially it was scheduled that participants in the study would come from primary health care, in the end only patients from tertiary health centers were included. Nevertheless, the different source of patients did not weaken the study's target to collect real life data and at the same time offered the possibility for a reliable clinical and laboratory evaluation. Another drawback of the study is that although the planned sample of patients was 300, only 186 were finally recruited due to investigators capability. This, in combination with the great number of patients lost to follow up as well as the absence of homogeneity in treatment strategies among investigators make data – especially those concerning efficacy – more difficult to interpret. Another caveat is that study data is quite old and this is the reason why only short term adverse events were investigated and data on long term adverse reactions – which would be of specific interest - are missing. Thus, another

study with a protocol applied strictly by all investigators and aiming to record rabeprazole long term safety data in Greek GERD population would be of great value.

In conclusion, the safety of rabeprazole in this study was comparable with the previously reported rabeprazole safety profile. Rabeprazole in the everyday health care setting was effective in reducing the symptoms of GERD, complicated or not, including the frequency and severity of heartburn.

Acknowledgements

Summary Box

What is already known:

- Various studies have shown that rabeprazole, a potent proton pump inhibitor, is effective and safe in the management of erosive or symptomatic GERD

What the new findings are:

- The present study confirms the safety profile of rabeprazole in Greek GERD population, as no new AEs were recorded
- The study has given data regarding GERD management with rabeprazole in real-life healthcare settings

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