Long-Term Efficacy of Rabeprazole in the Prevention of Relapse in Erosive GERD

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Background

- Gastroesophageal reflux disease (GERD) is a chronic condition characterized by prolonged exposure of the esophageal mucosa to acidic gastric contents, producing symptoms and esophageal erosions. The PPI, rabeprazole, has demonstrated rapid and potent acid suppression,[1,2] which suggests its efficacy in the prevention of relapse of erosive GERD.

Aims

- To compare the long-term efficacy and safety of once-daily rabeprazole 20 mg, 10 mg, and placebo in the prevention of relapse in patients previously diagnosed with erosive or ulcerative GERD.

Methods

- Two multicenter, double-blind, placebo controlled, parallel-arm maintenance trials enrolled a total of 497 patients with previously diagnosed and healed erosive or ulcerative GERD, who were randomly assigned to receive rabeprazole 20 mg or 10 mg or placebo once-daily in the morning.
- After successfully completing 1 year of treatment (defined as endoscopically verified maintenance of healing), patients continued in an extension phase for up to 4 years, for a total study duration of 5 years (260 wk). The extension phase was unblinded to the sponsor, but blinded to treating physicians, support staff, and patients. Endoscopies were performed at weeks 4, 13, 26, 39, and 52 in the first year and annually thereafter
- The primary efficacy variable was continued absence of esophageal erosions or ulcerations upon follow-up endoscopy over 5 years. Relapse was defined as a modified Hetzel-Dent grade of >2.
- Secondary safety variables included evaluation of safety up to 5 years, including adverse events (treatment-emergent signs and symptoms) and the incidence of enterochromaffin-like (ECL) cells, respectively.
- Data presented are for the intent-to-treat (ITT) population, last-observation-carried-forward (LOCF) analysis. Results were also analyzed by subset of baseline characteristics: age, race, gender, tobacco/alcohol/caffeine consumption, antacid use, heartburn frequency, day/night heartburn severity, and overall well-being.

Results

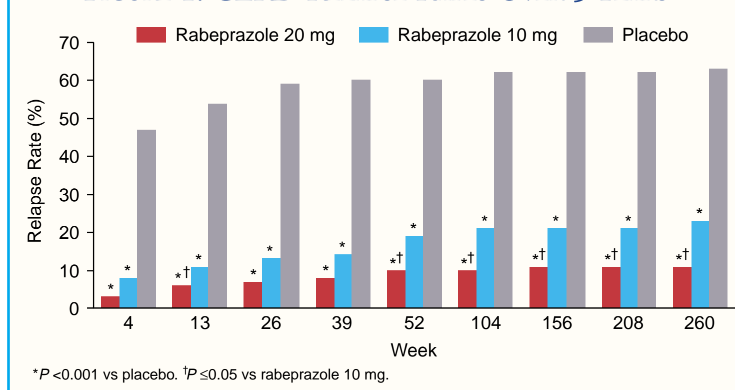
- There were no significant demographic differences between treatment and placebo groups (Table 1).

Table 1. Patient Demographics

Characteristic	N=497
Gender, n (%)	
Male	320 (64.4)
Female	177 (35.6)
Race, n (%)	
Caucasian	448 (90.1)
African American	31 (6.2)
Asian	4 (0.8)
Other	14 (2.8)
Age, mean years ± SD	53.93 ± 14.12
Weight, mean ± SD	188.12 ± 37.63
Antacid use, n (%)	126 (25.4)
Tobacco consumption, n (%)	109 (21.9)
Caffeine consumption, n (%)	369 (74.2)
Alcohol consumption, mean beverages/week ± SD	2.16 ± 6.39

- Erosion/ulceration relapse rate was significantly lower in the rabeprazole groups than in the placebo group at all time points from week 4 to endpoint (P <0.001) (Figure 1). In the rabeprazole 20-mg group, relapse rates never rose higher than 11%, compared with a high of 63% for the placebo group.

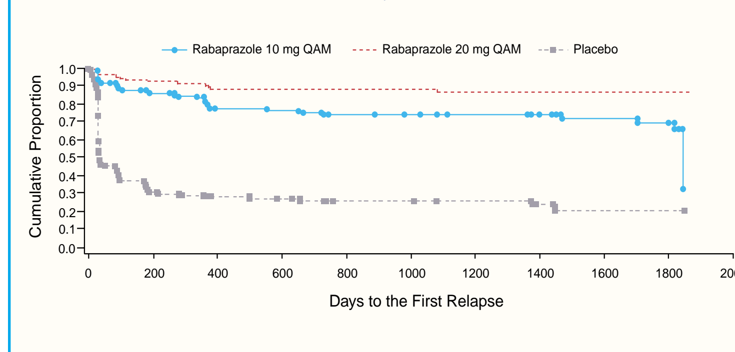
Figure 1. GERD Relapse Rates Over 5 Years



*P <0.001 vs placebo. †P ≤0.05 vs rabeprazole 10 mg.

- The GERD relapse rate that was observed at the 5-year endpoint was lowest in the rabeprazole 20-mg group (11%), greater in the rabeprazole 10-mg group (23%), and highest in the placebo group (63%). The difference in GERD relapse rates between the rabeprazole groups and the placebo group was statistically significant (P <0.001). Additionally, rabeprazole 20 mg was significantly superior to rabeprazole 10 mg (P=0.005).
- The probability of patients remaining healed at study endpoint based on Kaplan-Meier analysis was 87% for rabeprazole 20 mg, 33% for rabeprazole 10 mg, and 20% for placebo (Figure 2).

Figure 2. Cumulative Proportion of Patients Remaining in Remission: Days to First Relapse



- Time to median relapse was not achieved in the rabeprazole 20-mg group, and was reached in 1848 days and 32 days in the 10-mg and placebo groups, respectively (P=0.0001).
- Subset analyses demonstrated no statistically significant correlation between any baseline characteristic and relapse rate.
- Both doses of rabeprazole were well tolerated (Table 2).

Table 2. Most Frequently Reported Treatment-Related Signs and Symptoms Over 5 Years

	Rabeprazole 20 mg (N=163)	Rabeprazole 10 mg (N=165)	Placebo (N=169)
		n (%)	
Flu syndrome	37 (23)*	33 (20)*	12 (8)
Headache	35 (21)†	41 (25)*	21 (12)
Pain	29 (18)*	41 (25)*	10 (6)
Surgical procedure	33 (20)*	32 (19)*	6 (4)
Diarrhea	45 (28)*	45 (27)*	20 (12)
Pharyngitis	34 (21)*	35 (21)*	16 (9)
Rhinitis	54 (33)*	53 (32)*	21 (12)

*P ≤0.005 vs placebo. †P=0.029 vs placebo.

- Over the 5 years of study, there was a trend toward increased incidence of enterochromaffin-like (ECL) cells. However, no biopsy showed adenomatoid, dysplastic, or neoplastic changes in ECL cells.

Conclusions

- Rabeprazole 20 mg and 10 mg once daily in the morning were effective and well tolerated in the long-term maintenance of GERD healing.
- The 20-mg dose was more effective than the 10-mg dose in maintaining healing for 5 years.
- Increased incidence of ECL cells with treatment was not associated with significant pathology.

References

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