A review of rabeprazole in the treatment of acid-related diseases

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Abstract: Rabeprazole is a proton pump inhibitor. Pharmacodynamic data show rabeprazole can achieve optimal acid suppression since the first administration and can maintain this advantage in the following days of therapy. Moreover, rabeprazole has the highest pKa (~ 5.0, the pH at which a drug becomes 50% protonated), and hence the molecule can be activated at higher pH levels much faster than other PPIs. Due to its peculiar catabolic pathway, ie, a prevalent metabolism through a non-enzymatic pathway, rabeprazole is less susceptible to the influence of genetic polymorphisms for CYP2C19, resulting in minor influences on its pharmacokinetics and pharmacodynamics. In terms of clinical efficacy, rabeprazole 20 mg uid or 10 mg bid produced healing rates at 8 weeks similar to those obtained with omeprazole 20 mg uid in erosive esophagitis patients, and in NERD patients doses of 10 or 20 mg are equivalent and both are better than placebo at 2 and 4 weeks. To prevent symptomatic relapse, on-demand strategy with rabeprazole 10 mg daily appears to be ideal, due to its rapidity of onset; results on NERD patients have documented its superiority over placebo. Continuous treatment, however, up to 5 years, seems to achieve better results than on-demand therapy, particularly in patients with esophagitis. It is debated whether in the latter halved doses (10 mg) are really equivalent to full dose (20 mg). Rabeprazole has been used with success in the treatment of some atypical GERD manifestations, such as dysphagia associated with GERD, GERD-related asthma and chest-pain, and in the therapy of Barrett's esophagus. Finally, rabeprazole achieves similar *Helicobacter pylori* eradication rates compared with omeprazole and lansoprazole when co-administrated with low or high doses of antibiotics (amoxicillin and clarithromycin). In addition, low doses of rabeprazole (10 mg/bid) may be effective in eradicating the pathogen

Keywords: rabeprazole, acid-related disorders, gastro-esophageal reflux disease, *Helicobacter pylori* infection, pharmacodynamics, pharmacokinetics, therapeutic use

Introduction

Rabeprazole is a proton pump inhibitor (PPI) and as such covalently binds with and inactivates the gastric parietal cell proton pump (H^+/K^+-ATPase). This inhibits in turn gastric acid production and raises gastric pH. Proton pump inhibitors are indicated in the management of acid-related disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease, in association with *Helicobacter pylori* eradication therapy when needed.

Rabeprazole has been previously reviewed (Carswell and Goa 2001) and aim of the current review is to provide an update on the pharmacology and clinical profile of oral rabeprazole and its use in acid-related disorders, with particular focus on its role in GERD maintenance therapy, its use in Barrett's esophagus, and its cost-effectiveness.

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Pharmacology

Pharmacodynamics

The most effective way to increase the pH in the stomach, and hence to reach a therapeutic level for GERD, is the blockage of the proton pump enzymes in the parietal cells.

All PPIs, being substituted benzimidazoles, share the same antisecretory mechanism: to be activated, they concentrate in the secretory canaliculus of the parietal cell thanks to the acid milieu of the environment. The protonated molecules undergo a conversion to an active sulfenamide compound (the rate-limiting step) and, in this state, form covalent inhibiting disulfide bonds with surface-exposed cysteines of the active parietal cell H^+/K^+-ATPase.

However, the five available PPIs differ in terms of acid stability as the modified functional substituents on the two-ring structures give rabeprazole the highest pKa (~ 5.0, the pH at which a drug becomes 50% protonated), and hence the molecule can be activated at higher pH levels much faster than other PPIs: at pH 1.2 (the pH level of the canalicular space after meals) rabeprazole took 1.3 minutes to be half-activated in vitro, compared with 2.0, 2.8, and 4.6 min respectively for lansoprazole, omeprazole, and pantoprazole. At pH 5.1 (the pH during fasting), the activation half-life was again the shortest one for rabeprazole 7.2, 90, 84, and 282 min, respectively (Kromer et al 1998).

In an isolated hog vesicle model, rabeprazole confirmed its potent and fast onset of action: within 5 min of rabeprazole exposure the proton pump was near-maximally inhibited. The same target was reached after 30 min for lansoprazole and omeprazole; but pantoprazole could only inhibit the 50% of the pump by the end of the 50 minute test (Besancon et al 1997).

Therefore, rabeprazole sodium produces a dose-related sustained inhibition of both basal and peptone meal-stimulated gastric acid secretion (Lew et al 1998; Ohning et al 2003).

It is widely recognized that the antisecretory activity of PPIs is predictive of their efficacy in acid-related disorders. It has been shown that duodenal ulcer healing correlates with an intragastric pH >3 holding time of 18–20 hours, while erosive GERD healing with about a round-the-clock pH >4 holding time (Burget et al 1990; Bell et al 1992).

Recent work has confirmed the in vivo past evidence that rabeprazole can achieve optimal acid suppression since the first administration and can maintain this advantage in the following days of therapy, resulting in a higher median 24-hour intragastric pH and longer times with pH >3 and >4 compared with omeprazole (Williams et al 1998).

In 2003 Pantoflickova et al (2003) concluded that the higher pKa of rabeprazole might explain its major antisecretory effect of the former during the first 24 hours post-dose compared with the other PPI formulations tested. In a multiple crossover, comparative trial in 18 *H. pylori*-negative adults, rabeprazole 20 mg could reach a median 24-hour gastric pH of 3.4, compared with 2.9 for lansoprazole 30 mg, 2.2 for pantoprazole 40 mg, 1.9 for omeprazole 20 mg, 1.8 for omeprazole 20 mg MUPS (multiple unit pellet system), and 1.3 for placebo ($p < 0.05$ vs all other PPIs and placebo). In addition, rabeprazole maintained pH >4 for more time (8 hour) than the other agents (respectively 7.4, 4.9, 2.9, 3.0, and 0.9 hours, $p \leq 0.04$ for rabeprazole vs the others).

A full article (Warrington et al in 2002) presented the results of a study where rabeprazole was compared with esomeprazole on a mg-per-mg basis: in this randomized, two-way crossover study, 24 healthy volunteers received treatment for a total of 5 days separated by a 14-day washout period. On day 1 the mean 24-hour intragastric pH AUC and mean percentage 24-hour pH >3 and >4 holding times were statistically greater for rabeprazole 20 mg than for esomeprazole 20 mg. However, on day 5 the significant superiority was registered for only intragastric pH AUC ($p < 0.05$).

Tolman et al (2006) have recently observed that lansoprazole 15 and 30 mg has a greater acid-suppression activity than, respectively, rabeprazole 10 and 20 mg during hours 0–5 on days 1 and 5, whereas rabeprazole is equivalent or more effective during hours 11–24 on both days. In an open-label, randomized, crossover trial 72 healthy volunteers received each of the four treatments for 5 days with 2-week washout periods and underwent continuous 24-hour intragastric pH-metry on baseline, 1 and 5 days. Mean percentage time for pH >4 and mean 24-hour pH were overall comparable between the two PPIs on both days 1 and 5, except for rabeprazole 10 mg which was statistically superior to lansoprazole 15 mg.

A reduced dose of rabeprazole (10 mg od) exhibited better antisecretory activity than either omeprazole 20 mg od or lansoprazole 30 mg od in a study that analyzed the percentage of time pH ≥3 on each of the first three days of therapy in 8 *H. pylori*-negative CYP2C19 extensive metabolizers. On days 1, 2, and 3 the ratios were 13.6%, 35.3%, and 62.8% for rabeprazole 10 mg; 7.4%, 13.6%, and 26.6% for lansoprazole 30 mg; and 6.1%, 11.4%, and 16.4% for omeprazole 20 mg (Saitoh et al 2002).

Again rabeprazole 10 mg provided a faster acid inhibition compared with omeprazole 10 mg in a randomized, double-blind, placebo-controlled, three-way crossover study on 27 volunteers. By the end of the 7-day treatment, median gastric pH was significantly higher with rabeprazole than with omeprazole (3.7 vs 2.2, $p = 0.0016$) and the time with pH above 4 was more than doubled (10.5 vs 4.6 hours, $p = 0.0008$) (Bruley Des Varannes et al 2004).

A number of researchers during recent years have investigated the occurrence of nocturnal gastric acid breakthrough (NAB), which has been defined as the occurrence of intragastric pH dropping to below 4 for at least 1 hour during the 12 hours of night sleeping period, in GERD patients with nocturnal reflux symptoms and have questioned whether this phenomenon is due to a failing efficacy of PPIs over the 24 hours. In 2003 Pehlivanov et al (2003) demonstrated that rabeprazole 20 mg, administered in the morning or in the evening, significantly shortened the mean NAB duration versus the baseline recording (4.1 for rabeprazole a.m. and 3.4 for rabeprazole p.m. vs 7.8 for baseline, $p < 0.05$).

Rabeprazole has also shown (Luo et al 2003) to be more effective than first-generation PPIs in reducing the duration of NAB and, hence, increasing the nocturnal alkaline amplitude (NAKA), which has been defined as the occurrence of an abrupt increase in intragastric pH to above 4–6 after sleeping, mostly in the early morning. Forty patients with active peptic ulcer were randomly assigned to receive a single oral dose of rabeprazole 10 mg, omeprazole 20 mg, or pantoprazole 40 mg; the intragastric pH was monitored 1 hour before and 24 hours after the dose was given. In the rabeprazole group, the pH of NAB was statistically greater than the one in the others (1.84 vs 1.15 and 1.10 for respectively rabeprazole vs omeprazole and pantoprazole, $p < 0.01$). Rabeprazole also gave a longer time of NAKA (4.65 hours) than omeprazole (3.22 hours) and pantoprazole (3.15 hours), both $p < 0.05$ (Luo et al 2003). It must be acknowledged that in Luo's study the *H. pylori* status was not controlled, and this factor is known to influence the duration of NAB, as for example shown by the increase of NAB following *H. pylori* eradication (van Herwaarden et al 2000). It is possible that the newest PPIs, such as esomeprazole and the not yet marketed tenatoprazole, might be even better for control of NAB (Hunt et al 2005), although direct comparison with rabeprazole does not exist.

An important aspect that may influence the pharmacodynamics of PPIs is the CYP2C19 genotype status of patients. CYP2C19 is an isoenzyme of the cytochrome P450 involved in the catabolism of PPIs. As rabeprazole is less dependent on the polymorphism of this isoenzyme (see Pharmacokinetics section), its antisecretory activity is more predictable than that of the other PPIs, which are mainly catabolized through this isoenzyme. Adachi et al (2000) came to this conclusion when they investigated the intragastric pH in 20 *H. pylori*-negative volunteers during a 7-day dosing regimen with rabeprazole 20 mg od or lansoprazole 30 mg od. In the rabeprazole group, the median day-time and night-time pH was not influenced by CYP2C19 genotype; on the other hand, the median pH in poor metabolizers during lansoprazole administration was higher than in homozygous extensive metabolizers and heterozygous extensive metabolizers. The percentage of time with $pH < 4.0$ had a similar outcome to that of median pH.

Another aspect to take into consideration is the gastric pH profile, which has a regional variability in the stomach. It seems that this regional variability of pH profile, in particular the highly acid "pocket" observed close to the cardias, may be involved in the occurrence of postprandial heartburn in GERD patients. In 2001 Fletcher et al (2001) reported the presence of this acid pocket, after the meal, just below the gastro-esophageal junction. By using a dual pH-metry of the stomach, and a pull-through technique, they were able to show a pocket of acid at the gastroesophageal junction that extended from the cardias across the squamocolumnar junction 1.8 cm into the distal esophagus and escaped the buffering effect of meals, remaining highly acidic (median pH 1.6) compared with the body of the stomach (pH 4.7; $p < 0.001$). Fletcher et al hypothesized that the acid pocket is likely to contribute to the high prevalence of disease at this site. In a recent article, rabeprazole 20 mg, administered for 8 days in normal subjects, decreased the length, the magnitude, and the number of postprandial acid pockets. On day 1 and 8 the acid pockets were 62 and 50 in the placebo group, but 30 and 27 in the rabeprazole one (Vo et al 2005).

Considering the above data, it should be questioned whether for the purpose of acute therapy in GERD patients a reduced or a standard dose of PPI is more suitable to achieve optimal acid suppression (ie, an intragastric pH above 4 lasting for 20–22 hours a day), which is considered necessary to promote esophageal mucosal healing within 8 weeks. Shimatani et al investigated the acid-suppressive effects of rabeprazole, omeprazole and lansoprazole at reduced and standard doses. These authors performed a prospective, randomized, open-label, 8-way crossover study in 9 healthy *H. pylori*-negative CYP2C19 homozygous extensive metabolizers, each of one took either 10 or 20 mg rabeprazole; 10, 20, or 40 omeprazole; 15 or 30 mg lansoprazole; and placebo, all regimens once daily for 7 consecutive days with a washout period of at least 2 weeks. Compared with baseline data (7%), the median values of the 24-hour percentage of time with $pH > 4$ significantly increased, but none of the 7 regimens used was able to reach the ideal threshold. The percentages of this threshold were: 51% for rabeprazole 10 mg, 59% for rabeprazole 20 mg, 26% for omeprazole 10 mg, 48% for omeprazole 20 mg, 62% for omeprazole 40 mg, 34% for lansoprazole 15 mg, and 56% for

lansoprazole 30 mg. NAB was observed under all regimens, even if rabeprazole 10 and 20 mg kept intragastric pH >4 for a longer time than the respective doses of the other two PPIs (Shimatani et al 2006).

Finally, besides its antisecretory effect, rabeprazole 20 mg has been demonstrated to significantly enhance gastric mucin and mucus content, both in basal and pentagastrin-stimulated conditions (mucin content was: 0.82 and 0.96, respectively with rabeprazole vs 0.58 and 0.36 mg/mL, respectively with placebo, $p < 0.05$) (mucus content was 3.31 and 3.36 with rabeprazole vs 2.28 and 1.5 mg/mL with placebo, $p < 0.05$) as well as the viscosity of gastric juice (24.4 and 28.47 with rabeprazole vs 19.37 and 19.20 with placebo, $p < 0.05$). Similar data were observed during concomitant administration of rabeprazole and naproxene, as a result of a direct stimulatory action of rabeprazole on gastric mucous cells. In fact, co-administration of rabeprazole 20 mg prevented the naproxen-induced decline of gastric mucin and mucus secretion in 21 asymptomatic *H. pylori*-negative volunteers: during basal and pentagastrin-stimulated conditions, rabeprazole augmented the mucus production by 47% ($p = 0.003$) and 22%, and the mucin output by 40% ($p = 0.05$) and 67% ($p = 0.003$) respectively. This unique pharmacological property may exert a clinical benefit in protecting the upper alimentary tract mucosa (Skoczylas et al 2003; Jaworski et al 2005).

Pharmacokinetics

Rabeprazole is marketed as an enterically coated formulation, due to the instability of all PPIs in acid environment. After oral ingestion it is relatively rapidly absorbed as maximal plasma concentration (C_{max}) is reached between 2.8 and 5.1 postdose (Swan et al, 1999).

The pharmacokinetics of the molecule has been shown to be linear in the range 10–80 mg with an overall bioavailability of 52%, seen with rabeprazole 20 mg. Although C_{max} and area under the curve (AUC) of the plasma concentration are proportional to the dose ingested, time to reach C_{max} and half-life are dose-independent. This behavior confirms that rabeprazole does not have a saturable first-pass metabolism and it can be absorbed in high doses (Swan et al 1999).

Neither antacids nor food influence the bioavailability of the molecule, even if food intake delayed the absorption of rabeprazole 20 mg of about 1.7 h and reduced the apparent elimination half-life due to a probable delayed gastric emptying (Swan et al 1999).

Preclinical studies have demonstrated that rabeprazole's volume of distribution is 0.34 L/kg in a variety of tissues, including the gastric mucosa, stomach, kidney, bladder, liver, intestine, and thyroid. In healthy volunteers, it was demonstrated to be bound to plasma proteins 94.8%–97.5% (Swan et al 1999).

No significant accumulation occurs during repeated administration, as the elimination half-life is about 1 h after single and 1.5 h after multiple administrations. A 20 mg dose of rabeprazole is excreted approximately 90% in the urine (thioether carboxylic, glucoronide, and mercapturic metabolites) and 10% in the faeces (Swan et al 1999; Fuhr and Jetter 2002; Thjodleifsson 2004).

In terms of its elimination, rabeprazole is unique. Whereas other PPIs such as omeprazole, lansoprazole, esomeprazole, and pantoprazole are metabolized mainly by CYP2C19 in the liver, rabeprazole is metabolized mainly through a non-enzymatic pathway to rabeprazole-thioether and, to a much lesser extent, by the citochrome P450 isoenzymes CYP2C19 (demethylated rabeprazole) and CYP3A4 (rabeprazole-sulfone). It is known that there are genetically determined differences in the activity of this enzyme. The genotypes of CYP2C19 are classified into the three groups, rapid extensive metabolizer (RM), intermediate metabolizer (IM), and poor metabolizer (PM). The pharmacokinetics and pharmacodynamics of PPIs depend on CYP2C19 genotype status. Plasma PPI levels and intragastric pHs during PPI treatment in the RM group are lowest, those in the IM group come next, and those in the PM group are highest of the three groups. These CYP2C19 genotype-dependent differences in pharmacokinetics and pharmacodynamics of PPIs influence the cure rates for the gastro-esophageal reflux disease and *H. pylori* infection by PPI-based therapies. For the better PPI-based treatment, doses and dosing schemes of PPIs should be optimized based on CYP2C19 genotype status (Furuta 2005). The peculiar catabolic pathway implies that rabeprazole is less susceptible to the influence of genetic polymorphisms for CYP2C19, resulting in minor influences on its pharmacokinetics and pharmacodynamics.

The impact of CYP2C19 polymorphism on pharmacokinetics of rabeprazole, omeprazole, and lansoprazole was assessed in 18 Japanese subjects (6 homozygous metabolizers, 6 heterozygous metabolizers, and 6 poor metabolizers). AUC, C_{max}, and elimination half-life were not affected by CYP2C19 genotype for rabeprazole; however, AUC and C_{max} were increased in poor metabolizers for lansoprazole and omeprazole (Sakai et al 2001). This predictivity of rabeprazole has the potential to reduce interpatient variability in both pharmacological and clinical effects.

Patient genetic characteristics increased the intragastric pH after single and repeated doses in heterozygous extensive and poor metabolizers versus homozygous extensive metabolizers who took omeprazole 20 mg for 8 days. In the rabeprazole group the pH profile was almost consistent in the three genetic subgroups (Shirai et al 2001). A similar outcome was observed in patients with acid-related disease (Horn 2004).

As a result of CYP2C19 polymorphism, most Caucasians (60%–70% homozygous extensive metabolizers, 28%–36% heterozygous extensive metabolizers, and 2.7%–6.1% homozygous poor metabolizers) can rapidly metabolize PPIs such as omeprazole, esomeprazole, lansoprazole, and pantoprazole and show a diminished acid inhibitory activity of these PPIs among extensive metabolizers (Furuta 2005). This phenomenon might be masked by the observation that both omeprazole and esomeprazole inhibit the activity of CYP2C19 through their sulfone metabolite and, hence, actually autoinhibit their own metabolism, resulting in a non-linear increase in blood levels of these PPIs following repeat dosing. With omeprazole 20 mg, AUC increased by 173% and with esomeprazole by 190%–265% for the 20 and 40 mg doses respectively (McColl and Kennerley 2002).

The prevalent non-enzymatic metabolic pathway of rabeprazole is also the reason for the absence of drug–drug interactions between this PPI and other drugs, which are metabolized by the isoenzymes of the cytochrome P450. Co-administration of rabeprazole did not affect the pharmacokinetics of theophylline, diazepam, warfarin, and phenytoin (Thjodleifsson and Cockburn 1999). The expected interference with the pH-dependent absorption of digoxin and ketoconazole is common to all PPIs (Ishizaki and Horai 1999).

The aim of a recent Italian study was to evaluate the interactions of rabeprazole and two antibiotics, used in a 1-week eradication therapy, with hepatic metabolism in a clinical setting. Ten patients received an eradication regimen based on rabeprazole 20 mg/bid, clarithromycin 500 mg/bid, and metronidazole 500 mg/bid; in addition to this, they performed a ^{13}C-aminopyrine breath test at baseline (t_0), at the end of therapy (t_8) and after 1 month of follow-up (t_{38}). The percentage of the administered dose of ^{13}C recovered per hour (^{13}C-ABT dose/hour) and the cumulative percentage of the administered of ^{13}C recovered over time were quite similar at the three time points (^{13}C-ABT dose/hour: 14.0 ± 5.4, 13.5 ± 4.0, and 16.1 ± 5.6 respectively for t_0, t_8 and t_{38}; ^{13}C-ABT cumulative dose: 2.4 ± 1.1, 2.4 ± 0.8, and 2.6 ± 1.0 respectively for t_0, t_8, and t_{38}), confirming the absence of interactions of concomitant drugs at hepatic level (Giannini et al 2005).

Although the pharmacokinetic profile of rabeprazole is altered in the elderly (C_{max} increased by 60% and AUC doubled after a 7-day treatment with rabeprazole 20 mg) and in patients with mild to moderate compensated hepatic dysfunction (C_{max} increased by 50% and AUC doubled after a single dose of rabeprazole 20 mg), but not in patients with renal failure (after a dose of rabeprazole 20 mg on the day after hemodialysis and a second dose after a 2-week washout period during dialysis), no dosage adjustment is required in special populations, considering the evidence that these pharmacokinetic alterations were not associated with clinically significant abnormalities in laboratory parameters or serious adverse events (Fuhr and Jetter 2002). These findings are in contrast to those for H_2-receptor antagonists, wherein dosage adjustements are indicated if patients have moderate to severe renal function impairment (Feldman and Burton 1990) but not in contrast with those for other PPIs.

Clinical efficacy profile in GERD

GERD is a common disease affecting a large part of Western population and progressively increasing in Eastern societies. There is an ongoing debate as to whether the different manifestations of prolonged reflux of gastric content in the esophagus should be interpreted as a disease continuum (Pace and Bianchi Porro 2004) or as different and non-communicating sub-groups (Fass and Ofman 2002). This debate is not only of theoretical relevance, because different natural courses of disease mean different expectations from the drugs we test against GERD, which in turn may affect the way we plan clinical studies. The ability to prevent the development of erosions in patients with symptoms, but without esophagitis (non-erosive reflux disease, NERD), would be a strong endpoint for those considering GERD as a spectrum disease, while those who consider GERD an umbrella covering different non-communicating diseases would possibly not even consider the possibility of progression to erosive disease. When possible, we will consider GERD as a spectrum disease, which has milder, non-erosive cases and longer lasting, worse, erosive or complicated cases. Data on atypical and extra-esophageal symptoms will be included as well. An extensive review (Carswell and Goa 2001) covered these topics in 2001 and we will focus only on papers published after that date.

GERD is associated with several symptoms, such as heartburn, belching, and regurgitation, which arise from esophageal exposure to gastric acid. Symptoms may occur with or without the presence of endoscopically observed esophageal mucosal damage and inflammation. NERD pa-

tients represent the majority of those who present with GERD symptoms. Although acid suppression therapy is a logical approach to relieve GERD symptoms, it has been thought to be less successful in patients with endoscopically negative or symptomatic GERD, than in those with erosive GERD. Some suggested (Gardner et al 2003) that this might be due to a decreased response to antisecretory agents in the postprandial period shown by NERD subjects.

Non-erosive GERD

Miner et al (2002) report the results of a placebo-controlled, double blind study conducted on 203 patients with NERD and moderately severe GERD symptoms. After a 2-week, single-blind, placebo run-in phase, patients were randomized to receive 10 mg or 20 mg of rabeprazole or placebo once daily for 4 weeks. Both doses of rabeprazole rapidly and effectively relieved heartburn, with significant improvements on day 1 of dosing, and an improvement of other GERD-related symptoms, including regurgitation, belching, bloating, early satiety, and nausea. Both doses were well tolerated without significant difference among the two, but with a significant superioriority over placebo with respect to time to the first 24-hour heartburn-free interval (2.5 and 4.5 days for 10 mg and 20 mg of rabeprazole, respectively, vs 21.5 days for the placebo), first day-time or night-time heartburn-free interval (1.5–3 days for rabeprazole groups vs 12.5–15 days for the placebo), as well as to percentage of heartburn- and antacid-free time (Miner et al 2002).

Another paper reported on the positive effects of rabeprazole therapy on GERD-related symptom distress, as measured with the GERD Symptom Assessment Scale (GSAS) (Damiano et al 2003). This scale was applied in two randomized, placebo-controlled trials of rabeprazole among patients with NERD. The age (mean ± SD) of the 223 patients was 43.5 ± 11.9 years, and most were female (67%) and Caucasian (78%). Significantly greater reductions in symptom distress were observed among patients receiving rabeprazole 20 mg daily for 4 weeks in comparison with those receiving placebo (–0.62 vs –0.36, $p < 0.0001$). The magnitude of this treatment-induced difference in GSAS was comparable with the differences in patient-perceived global rating (0.2 and 0.3 points, $p < 0.0001$).

A further study published by Kahrilas et al (2005) assessed the rapidity of symptom relief and 4-week efficacy of rabeprazole 20 mg in patients with moderately severe NERD, collecting data from 2 similarly designed, double-blind, placebo-controlled, multicenter, US trials. Two hundred and sixty-one patients were randomized to 4 weeks of rabeprazole 20 mg once daily or placebo and were asked to score and daily record symptoms in diaries. Median time to first 24-hour heartburn-free interval was significantly shorter for the rabeprazole group than for the placebo group (3.5 days vs. 19.5 days, $p \leq 0.0002$). Complete heartburn relief at week 4 was 32% with rabeprazole and 3.8% with placebo ($p \leq 0.001$). Regurgitation, belching, and early satiety were also significantly improved by week 4 of rabeprazole treatment, with a $p \leq 0.05$.

Fock et al (2005) studied the efficacy of rabeprazole vs esomeprazole in Asian patients with NERD, in a double-blind study. One hundred and thirty-four patients with typical symptoms and normal endoscopy received either rabeprazole 10 mg or esomeprazole 20 mg once daily for 4 weeks and kept daily diaries of symptoms, rating their severity. In this study rabeprazole 10 mg and esomeprazole 20 mg were comparable after 4 weeks of treatment with regard to the speed of action (time to achieve 24-hour symptom-free interval) for heartburn (8.5 vs 9 days) and regurgitation (6 vs 7.5 days) and patient's global evaluation at 4 weeks (96% on rabeprazole reported symptoms improvement vs 87.9% on esomeprazole, with p = NS). Satisfactory relief of day- and night-time symptoms was achieved in 98% of patients receiving rabeprazole and 81.4% of patients receiving esomeprazole, although the difference was not statistically significant.

NERD shows a definite tendency to relapse over time, similarly to the erosive form. Therefore the debate as to the optimal maintenance therapy for NERD is open. A logical consequence of the step-down treatment modality seems to be on-demand therapy (Pace et al 2002), which requires ideally a drug with a rapid onset of action. Unfortunately, there are very few studies comparing different PPIs used on-demand, with the only exception of a head-to head comparison of omeprazole with lansoprazole (Johnson et al 2002). Rabeprazole might prove to have some characteristics of an ideal PPI in regards to on-demand therapy, since the intragastric pH during the first 5–6 hours after a single dose of 20 mg rabeprazole is higher than after a single dose of 20 mg omeprazole, in particular in *H. pylori*-negative men who are CYP2C19 homozygous or heterozygous extensive metabolizers (Inamori et al 2003).

In 2004 Ponce et al (2004) published a paper concerning on-demand therapy with rabeprazole in erosive and non-erosive gastroesophageal reflux disease. The effects of therapy were analysed in terms of efficacy (absence of symptoms in a clinical questionnaire), health-related quality of life (HRQoL calculated with the SF-36 questionnaire) and

patient satisfaction measured with a visual analogue scale. Fifty-five patients (17 with NERD and 38 with low-grade esophagitis) were treated with rabeprazole 20 mg/day and those, healed clinically after 4 weeks (n = 51), took the medication in an on-demand way for 6 months. At the end of the study symptom control (heartburn < twice a week) had been achieved in over 85% of the patients. The mean (SD) amount of PPI used was 0.3 (0.19) tablet/day. The patient satisfaction score at the end of the acute phase was 98 (range, 0–100) and remained high (90; range, 10–100) and stable during on-demand therapy. Short-term treatment normalized the HRQoL scores, which were subsequently maintained during on-demand therapy.

A possible endpoint for on-demand therapy is to measure the time to unwillingness to continue treatment, although the validity of such a parameter has been questioned (Bytzer et al 2004). During 2004 were published the results of a multicenter, randomized, double-blind, placebo-controlled, withdrawal study comparing 6 months of on-demand treatment with rabeprazole 10 mg vs placebo. Adults with a history of reflux symptoms, a negative endoscopy and 3 days or more of moderate to very severe heartburn in the 7 days before enrollment (n = 535) entered 4 weeks of open-label, acute treatment with rabeprazole 10 mg once daily. Eighty-three per cent of patients reported complete symptom relief and then entered the 6 months on-demand phase. During on-demand treatment, rates of discontinuation because of inadequate heartburn control were 20% for placebo vs 6% for rabeprazole ($p < 0.00001$). Not surprisingly antacid use was two-fold higher in the placebo group than in the rabeprazole group ($p = 0.0009$).

Bour et al (2005) published a comparison of on-demand vs continuous long-term treatment of GERD and NERD with rabeprazole in patients with frequent symptomatic relapses. It was an open-label study, enrolling patients with mild erosive (Savary-Miller classification grades 1 or 2) and non-erosive reflux disease and frequent symptomatic relapses of at least moderate intensity in the previous year. After a 4-week selection phase with rabeprazole 10 mg once daily, patients reporting symptom relief were randomized to either rabeprazole 10 mg continuous treatment or on-demand treatment for 6 months. One hundred and seventy-six patients were enrolled in the selection phase (men, 53%; mean age, 49 years; non-erosive reflux disease, 36.4%; grade 1 esophagitis, 53.4%; grade 2 esophagitis, 10.2%) and rabeprazole relieved symptoms in 88.6%. Of this group, 152 were randomized to the comparative phase (continuous treatment, n = 81; on-demand treatment, n = 71). After 6 months symptom relief (2 points reduction on the symptoms rating scale) was slightly higher, 86.4% vs 74.6%, for patients in the continuous treatment group compared with those in the on-demand treatment group, but the difference was not statistically significant ($p = 0.065$), as for the overall quality of life score. As expected, daily consumption of rabeprazole was significantly lower in the on-demand treatment group than in the continuous treatment one (0.31 tablets vs 0.96 tablets; $p < 0.0001$).

Comparability problems of these studies on on-demand treatment are due to a variable mix of GERD and NERD patients, to the definition of on-demand treatment and to different length of run-in periods.

Erosive reflux disease (ERD)

In patients with erosive GERD, primary endpoints are the rate of endoscopically confirmed healing of ulcers and erosions and the decrease of frequency and severity of heartburn and associated GI symptoms. In the various studies reviewed, patients had endoscopically confirmed esophagitis and all were adults. Standard exclusion criteria included recent treatment with therapeutic doses of a proton pump inhibitor or histamine H_2-receptor antagonist, concurrent systemic disorders and medical conditions that would prevent endoscopy. There was no common attitude towards *H. pylori* testing and attempt at eradication.

Healing of esophagitis and symptom relief in ERD patients

Previously available literature (Dekkers et al 1999) indicated that rabeprazole 20 mg uid or 10 mg bid produced similar healing rates at 8 weeks, about 90%. Four-week healing rates paralleled these findings, and most data suggested that the majority of patients responding to treatment did so already after 4 weeks. Rabeprazole and omeprazole were of similar efficacy in relieving symptom frequency and severity at all timepoints, and their effect on overall well-being, as measured by the General Well-Being Schedule, appeared to be similar (Dekkers et al 1999; Caos et al 2000). In order to assess the relief from heartburn and from other symptoms of GERD after 3 days of treatment with standard-dose rabeprazole or high-dose omeprazole, healing rates and quantification of antacid use, Holtmann et al (2002) studied 230 patients with endoscopically confirmed erosive esophagitis that were randomized to receive 4 weeks of double-blind treatment with rabeprazole (20 mg) or omeprazole (40 mg). Patients who were not healed after 4 weeks received a further 4 weeks of treatment. There were no significant differences between the two groups concerning the number of patients with

relief from heartburn on day 4 (84% for rabeprazole; 95% confidence interval (CI), 76%–90%; 83% for omeprazole; 95% CI, 75%–89%) and from other gastro-esophageal reflux disease symptoms or in healing rates. During the first 3 days patients in the omeprazole group reported more frequently severe symptoms (day-time heartburn: 4.7% for rabeprazole vs 10.3% for omeprazole, $p = 0.005$; night-time heartburn: 4.7% for rabeprazole vs 9.8% for omeprazole, $p = 0.01$; statistical comparisons defined post hoc).

Robinson et al (2002) studied the onset of symptom relief with rabeprazole in a community-based, open-label assessment of patients with erosive esophagitis, enrolling 2579 patients to receive rabeprazole (20 mg uid for 8 weeks). Symptoms were rated daily by patients through an interactive voice response system. On day 1, rabeprazole significantly decreased day-time and night-time heartburn severity, regurgitation, and belching. Complete relief of day-time and night-time heartburn were 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. Patients with moderate or severe heartburn symptoms at baseline achieved an even greater degree of satisfactory symptom relief (none or mild) from day 1 onwards. The median time to satisfactory heartburn relief was 2 days. Subgroup analyses showed no consistent differences in efficacy compared to the overall population treated. Health-related quality of life in patients was significantly lower than that of the US general population and improved significantly after 8 weeks of rabeprazole therapy. Rabeprazole was well tolerated, with headache as the most common adverse event, reported by less than 2% of the study population.

In order to identify any difference in the speed of reflux esophagitis symptoms relief with omeprazole, lansoprazole, and rabeprazole, 85 patients with erosive reflux esophagitis were randomized to receive omeprazole 20 mg uid, lansoprazole 30 mg uid, or rabeprazole 20 mg uid for 8 weeks (Adachi et al 2003), and daily symptoms were assessed in the first 7 days of administration. The mean heartburn score decreased more rapidly in patients receiving rabeprazole than the other PPIs. Patients receiving rabeprazole reached also earlier complete heartburn remission (rabeprazole vs omeprazole: $p = 0.035$, rabeprazole vs lansoprazole: $p = 0.038$ by log-rank test). No differences were seen in the rate of endoscopic healing of reflux esophagitis at 8 weeks between the three treatment regimens.

Our group presented in 2005 (Pace et al 2005) the results of a study conducted in 560 Italian patients with Savary-Miller grade I-III reflux oesophagitis who were randomized in a double-blind, double-dummy fashion to rabeprazole or omeprazole 20 mg once daily for 4–8 weeks. At 4 to 8 weeks of treatment, healing rate was 97.9% in the rabeprazole group and 97.5% in the omeprazole one ($p < 0.0001$ at Blackwelder test), but time to the first day with satisfactory heartburn relief was shorter with rabeprazole than with omeprazole (2.8 ± 0.2 vs 4.7 ± 0.5 days, respecitively, $p = 0.0045$ at log-rank test). The Blackwelder test is a test to prove statistically equivalence (ie, non-superiority) among two treatments.

In a 8-week, prospective, multicenter, postauthorization surveillance study conducted in Greek clinical practices, and published by Archimandritis et al (2005), 273 patients with ERD were treated with rabeprazole 20 mg once daily for 4 to 8 weeks. GERD symptom severity on day 1, 2, 3, and 7 was measured using a 5-point scale and esophageal healing was evaluated performing endoscopy at baseline and after 4 and 8 weeks of treatment. Already on day 1 of treatment, rabeprazole obtained a statistically significant ($p = 0.0001$) improvement in heartburn, regurgitation, epigastric pain, and dysphagia across all grades of oesophagitis. Erosions healing rate was 77% at week 4 and 90% at week 8.

Relapse prevention

Studies included in this section were randomized and double-blind, and required patients to have had a previous diagnosis of erosive GERD healed within 90 days of enrolment, as demonstrated by endoscopy. At baseline endoscopy requirements included the absence of active erosions or ulcerations. The primary efficacy endpoint in studies was the continued absence of esophageal erosions or ulcerations at follow-up endoscopic examinations.

An early study compared rabeprazole with placebo (Birbara et al 2000), while a later one compared the daily dose of rabeprazole 20 mg with 10 mg (Caos et al 2000), and another one compared rabeprazole at the doses of 10 and 20 mg daily with omeprazole (Thjodleifsson et al 2000). Relapse rates after 1 year of treatment were similar (about 5%) with rabeprazole 10 or 20 mg/day and omeprazole 20 mg/day in one study (Thjodleifsson et al 2000), while significantly different between rabeprazole 10 and 20 mg/day (10% vs 27%; $p < 0.04$) in the other (Caos et al 2000). No significant differences between regimens were observed in secondary efficacy variables such as frequency and severity of heartburn, overall well-being, time lost from usual activities of daily living, or antacid use. These studies reported also Kaplan-Meier probabilities for remaining free of severe day-time and night-time heartburn. Patients receiving rabeprazole were significantly more likely to

remain free of severe heartburn after one year of treatment than those receiving placebo in one trial ($p < 0.0001$) (Caos et al 2000) and there were no significant differences between omeprazole and rabeprazole reported in the other (Thjodleifsson et al 2000).

A previous meta-analysis of comparative studies between PPIs (Dean et al 2001) included data from 1 unpublished study and 9 published studies, and indicated rabeprazole as more effective than other two proton pump inhibitors in preventing symptom recurrence in patients with GERD. The predicted recurrence rate for rabeprazole 20 mg/day was 0.14 (95% CI, 0.05–0.23) vs 0.32 (95% CI, 0.17–0.48) for lansoprazole 30 mg/day and 0.19 (95% CI, 0.07–0.32) for omeprazole 20 mg/day. Rabeprazole prevented 86% of symptom recurrences compared with 81% for omeprazole and 68% for lansoprazole. The authors of the study noted that these data were derived from only a small number of randomized trials and thus might overestimate the true level of efficacy of each drug.

The data concerning on-demand maintenance therapy have already been noted above (section on NERD).

In our study (Pace et al 2005) 560 patients with Savary-Miller grade I-III reflux oesophagitis were endoscopically healed and symptomatically relieved with PPI treatment and then openly maintained with rabeprazole 10 mg uid, (or bid in the event of clinical and/or endoscopic relapse), for a maximum of 48 weeks. During this maintenance phase, an endoscopic and/or clinical relapse was observed in 15.2% of patients.

Considering that few trials of proton pump inhibitors in maintaining healing of erosive or ulcerative GERD are conducted for longer than 1 year, Thjodleifsson and colleagues in 2003 (Thjodleifsson et al 2003) published the comparison of the efficacy and safety of 2 doses of rabeprazole with 20 mg omeprazole in the maintenance treatment of erosive GERD over 5 years. Two hundred and forty-three patients who had previously responded to acute treatment for erosive GERD were prospectively randomized to receive 5 years of treatment with rabeprazole (10 or 20 mg daily) or omeprazole (20 mg daily). The primary outcome measure was endoscopically confirmed relapse of erosive GERD. One hundred and twenty-three patients (51%) completed all 5 years of the study, with similar completion rates in the three groups. Relapses occurred in 9 of 78 (11.5%), 8 of 82 (9.8%), and 11 of 83 (13.3%) patients in the rabeprazole 20 mg, rabeprazole 10 mg and omeprazole 20 mg groups, respectively. Gastric biopsy showed no evidence of any harmful effects. All treatments were well tolerated.

In 2005 Caos et al (2005) presented the results of a 5-year maintenance study in 497 patients previously diagnosed with erosive/ulcerative GERD and healed in an acute efficacy trial, receiving once-daily doses of 10 or 20 mg rabeprazole or placebo. After 5 years, relapse rates in the placebo group were significantly higher than in both rabeprazole groups (placebo 63%, rabeprazole 20 mg 11%, rabeprazole 10 mg 23%, $p < 0.001$). The relapses in the two dosages groups were also significantly different ($p = 0.005$). Both rabeprazole doses were significantly superior to placebo in preventing relapse of heartburn frequency and improving patient quality of life. Analyses of adverse events, biopsy findings and laboratory values showed no evidence of clinically significant effects.

Barrett's esophagus (BE)

Some studies assessed the question concerning the effects of PPI therapy on esophageal acid and bile exposition, in an attempt to evaluate the proper PPI therapy in this subset of patients.

To evaluate oesophageal acid exposure in a large BE population and determine clinical factors predicting normalization of intra-oesophageal pH, 46 BE patients on rabeprazole twice a day therapy were studied using 24-hour pH monitoring (Wani et al 2005). Median total percentage time $pH < 4$ was 1.05% (range: 0%–29.9%) in the entire group and respective values for upright and supine percentage time $pH < 4$ were 1.15% and 0%. However, 34 of the BE patients (73.9%) had a normal pH study (median total percentage time $pH < 4$: 0.2%) and 12 patients (26.1%) had an abnormal result (median total percentage time $pH < 4$: 9.3%). There were no significant differences between patients with a normal and abnormal 24-hour pH result with respect to age, BE length, hiatal hernia size and presence of *H. pylori* infection.

Another prospective study (Gerson et al 2005) was conducted in BE patients already on PPI therapy in order to determine whether a shift to rabeprazole at a dose titrated for symptom relief could alter intra-oesophageal and intragastric acid suppression. Seventeen *H. pylori*-negative BE patients were studied with 24-hour pH monitoring for a first time during omeprazole or lansoprazole therapy, and for a second time on rabeprazole. Ten out of 17 (59%) patients had abnormal baseline intra-esophageal pH profiles under omeprazole or lansoprazole and 8 out of 10 were still abnormal on rabeprazole. Intra-gastric pH was out of control in all the BE patients, who demonstrated the phenomenon of nocturnal acid breakthrough, and a mean time with intra-gastric pH below 4.0 of 46% on omeprazole, 71% on lansoprazole, and 51% on rabeprazole ($p = 0.25$).

Elimination of acid reflux, confirmed by means of 24-hour esophageal pH-monitoring, was achieved using 40 mg rabeprazole 3 times per day in a recent study (Johnston et al 2005) planned to evaluate the safety and the efficacy of a new cryogenic device to perform endoscopic Barrett's mucosa ablation. In that study 11 subjects were treated with disappearance of BE in 78% patients and no subsquamous specialized intestinal metaplasia at the 6-month follow-up. These preliminary results show that cryoablation of BE under direct endoscopic visualization is safe and easy to perform and suggest that it could be a treatment modality worth further exploration in the ablation of GI mucosal lesions such as BE.

Atypical (or extra-esophageal) symptoms

Although considered a relevant problem in gastroenterology, the therapy of atypical or extraesophageal manifestations of GERD has been subjected to considerably less studies than the typical manifestations. In particular, direct comparison of PPIs are generally lacking; as an example, in the recent Cochrane review on the therapy of GERD-induced asthma with antisecretory agents (Gibson et al 2003), all PPI studies were placebo-controlled.

The studies with rabeprazole conducted on atypical GERD manifestations include the treatment of dysphagia, chest pain, laryngitis and GERD-induced respiratory and sleep disorders; most of them are open-label and uncontrolled studies.

To determine whether dysphagia associated with GERD could be effectively treated with rabeprazole, 68 outpatients with gastroesophageal reflux-associated dysphagia (Oda et al 2005) were studied with upper endoscopy (52 out of 68 had esophagitis) and then treated with rabeprazole 20 mg daily for 8 weeks. A further 6 months of treatment at 10 mg/day were warranted for those 16 subjects whose dysphagia improved. At the sixth month dysphagia was completely resolved in 40 subjects, improved partially in 20, and was unchanged in 8 subjects. Comparison between complete therapeutic successes and partial or total failures demonstrated that only improvement in heartburn symptoms seemed to correlate with efficacy of rabeprazole on dysphagia.

The use of rabeprazole in the empirical diagnosis of GERD-related chest-pain (the so called PPI test) has been assessed in a recent (Dickman et al 2005) double-blind, randomized, placebo-controlled, crossover trial, that demonstrated a sensitivity of 75% and a specificity of 90% for rabeprazole 20 mg bid, administered for 7 days in a therapeutic trial.

Treatment with rabeprazole 20 mg/day has shown to improve by more than 20% the peak expiratory flow (PEF) in 40% of asthma patients also suffering from GERD (Tsugeno et al 2003). The probability of getting a clinically relevant improvement in PEF with rabeprazole therapy is related to the intensity of GERD symptoms and the lack of steroid-dependency of asthma. The findings of another study (Oribe et al 2005) show that rabeprazole, but not histamine H_2-blockers, can directly decrease cough reflex hypersensitivity induced with an antigenic aerosol in guinea-pigs and elicited after 24 hours with capsaicin. Noteworthy, rabeprazole does not act reversing the pH drop in the bronchial washing fluid observed in antigen-challenged animals.

GERD is associated also with lower sleep quality. One week of therapy with 20 mg rabeprazole bid in GERD patients ameliorates subjective measures of sleep quality and overall acid reflux, but not objective sleep measures and night-time acid contact, as shown by polysomnography and 24-hour pH monitoring (Orr et al 2005).

Another well-known extraesophageal manifestation of GERD is chronic laryngitis. An open label study (Klopocka et al 2004) tried to estimate the efficacy of 2 months of 20 mg rabeprazole bid treatment in patients with long history of chronic idiopathic laryngitis, but without typical GERD symptoms. There was remarkably good therapeutic outcome, with hoarseness and pharyngeal pain resolved, respectively, in 68.7% and 78.5% of patients and laryngeal signs in 50%–80%. However, weak tension of vocal cords, which was often seen in these patients before the trial, persisted. A double-blind, randomized trial (Steward et al 2004) comparing 2-month lifestyle modification therapy plus rabeprazole 20 mg bid or placebo in chronic GERD-related laryngo-pharyngitis deserves careful examination. In this study good compliance with lifestyle modification significantly improved laryngo-pharyngitis symptoms, but adding rabeprazole did not significantly improve typical reflux symptoms, health status, or laryngeal appearance. The only two factors predicting good outcome on laryngeal symptoms seemed to be a good compliance to lifestyle modification and a positive effect on typical symptoms. Possible studies with 24-hour esophageal impedance monitoring in ear, nose, and throat of patients might allow stratifying these patients and defining standard length of treatment and more objective outcome measures.

Another study, again open-label and uncontrolled (Swiatkowski et al 2004), was conducted to estimate the effects of gastric acid output suppression with rabeprazole on course of angina pectoris and the results of the treadmill stress test in patients with coronary artery disease. In stable angina cases

rabeprazole 20 mg bid significantly decreases the frequency of angina-like chest pain and improves the results of the treadmill stress test, which implies that at least some of their symptoms are related to GERD.

Helicobacter pylori eradication and peptic ulcer healing

Considering the fact that many publications have appeared on the subject, our aim is to highlight only the most significant data published in recent years. A systematic review by Gisbert et al (2003) evidenced that rabeprazole achieves similar *H. pylori* eradication rates compared with omeprazole and lansoprazole when co-administrated with low or high doses of antibiotics (amoxicillin and clarithromycin). In addition to this, as shown by the above-reported review, low doses of rabeprazole (10 mg/bid) may be sufficient to eradicate *H. pylori* when administered with two antibiotics.

These results are consistent with data from Di Mario et al (2003). Ninety-four *H. pylori*-positive patients with dyspeptic symptoms were equally randomized to receive a 1-week regimen based on rabeprazole 10 mg/bid or 20 mg/bid plus clarithromycin 500 mg/bid and tinidazole 500 mg/bid. An urea breath test, performed 2 months after the end of the therapy, evidenced a comparable eradication rate between the two groups: 89.3% for rabeprazole 10 mg and 91.4% for rabeprazole 20 mg (p = ns).

Although a 7-day scheme is the optimal treatment to achieve good eradication rates, some authors have demonstrated that rabeprazole is also effective with shorter regimens. In 128 dyspeptic patients rabeprazole 20 mg/bid, together with clarithromycin 250 mg/bid and metronidazole 500 mg/bid, achieved 81% and 88% (respectively intention-to-treat and per-protocol analysis) eradication rates with a 4-day regimen vs 78% and 85% after a 7-day treatment (Gambaro et al 2003).

Yang and Giannini showed, separately, that the rabeprazole-based triple therapy could be shortened to 4 days without reducing its efficacy. In the work of Yang et al (2003) the intention-to-treat and the per-protocol analysis demonstrated that rabeprazole 20 mg/bid + clarithromycin 500 mg/bid + amoxicillin 1000 mg/bid eradicated the *H. pylori* infection in 87% and 91% of patients after 4 days of therapy in comparison with 83% and 95% for rabeprazole 20 mg/bid and with 88% and 100% for omeprazole 20 mg/bid after a 7-day regimen.

Giannini et al (2006) investigated 85 patients, who failed at least one *H. pylori* eradication before being randomized to receive rabeprazole 20 mg/bid + levofloxacin 500 mg/bid + tinidazole 500 mg/bid either for 4 or 7 days. The cure rate was, respectively, 83% in both intention-to-treat and per-protocol analysis for the 4-day scheme and 84% and 86% for the 7-day one.

Wang et al (2005) showed that a very short-term eradication regimen could be an optimal strategy; they prospectively evaluated 115 patients with *H. pylori*-infected active peptic ulcer, treating them with an even shorter triple therapy. Patients received in an open and random design the following scheme: rabeprazole 20 mg + clarithromycin 500 mg + amoxicillin 1000 mg all twice daily for 3 or 7 days; afterwards, all patients took rabeprazole 20 mg/uid until the eighth week. Three months after the therapy, the infection was cured in 84.6% vs 87.5% of patients, respectively (per-protocol analysis, p = 0.68). One year after the therapy, 75 patients repeated the urea breath test, confirming an eradication rate of 78.4% vs 81.6% for the 3- and 7-day regimen (per-protocol analysis, p = 0.73).

In the United States previous guidelines recommended a 10- to 14-day treatment due to scarcely reproducible data from 7-day American trials. Vakil et al (2004) showed that a 1-week therapy with rabeprazole 20 mg/bid, together with clarithromycin 500 mg/bid and amoxicillin 1000 mg/bid, is as effective as a 10-day rabeprazole- or omeprazole-based regimen in eradicating the infection. This was a double-blind, randomized, parallel-group trial, investigating 803 patients with or without peptic ulcer. A urea breath test, performed 6 weeks after the end of the therapy, assessed a cure rate of 77% for the 7-day rabeprazole-based regimen compared with 78% and 73% for the 10-day rabeprazole- or omeprazole-based therapy.

A recent publication has evidenced the reproducible eradication rates of rabeprazole between subjects with different hepatic metabolism due to CYP2C19 polymorphism. One hundred and eighty-seven *H. pylori*-infected peptic ulcer patients were randomly treated with either rabeprazole 10 mg/bid or lansoprazole 30 mg/bid plus amoxicillin 750 mg/bid and clarithromycin 400 mg/bid for 1 week. The eradication rates in the RAC and LAC groups were 75%, and 69% respectively, in the intention-to-treat analysis, and 80% and 75% respectively, on a per-protocol basis. When stratified for CYP2C19 polymorphism, the cure rate in RAC extensive metabolizers was less affected by variability than that in LAC ones: 86%, 91%, and 86% respectively for homozygous extensive metabolizers, heterozygous extensive metabolizers and poor metabolizers in the RAC group, compared with 74%, 83%, and 100% respectively for the same

subgroups of metabolizers in the LAC group (the data were obtained in subjects with strains sensitive to clarithromycin) (Kawabata et al 2003).

In 2005 Gisbert and Pajares (2005) questioned if a 1-week PPI-based triple therapy is enough to heal peptic ulcer. They performed a systematic review of 24 studies (2342 patients) where peptic ulcer healing was assessed in 1289 patients after just a 7-day PPI-based triple therapy. In addition to this they evaluated trials through a meta-analysis, comparing the efficacy on ulcer healing of this regimen vs the same scheme, but prolonging the PPI for a further 2–4 weeks. The authors concluded that a 7-day triple therapy is sufficient to promote ulcer healing; in fact, the healing rate was 86% and 95%, respectively, in all patients (both with *H. pylori* eradication success and failure) and in patients successfully eradicated. Two or more weeks of prolonged PPI therapy did not ameliorate these figures (91% with only 1 week of triple therapy vs 92% with prolonged PPI treatment, odds ratio = 1.11, 95% CI, 0.71–1.74).

Rabeprazole was demonstrated to be as effective as omeprazole in healing duodenal ulcer after a 1-week triple therapy. One hundred and seventy-three patients received in a random way rabeprazole 20 mg for 3 days or rabeprazole 10 mg for 7 days plus amoxicillin 1000 mg and clarithromycin 500 mg (RAC therapy) or omeprazole 20 mg for 7 days plus amoxicillin 1000 mg and clarithromycin 500 mg (OAC therapy) (all drugs twice daily). Six weeks after the end of treatment the endoscopy evidenced duodenal ulcer healing in 73% of 3-day RAC group and 89% of both 7-day RAC and OAC groups (intention-to-treat analysis). In the per-protocol population the rates were comparable, respectively 73%, 100%, and 89%. The *H. pylori* infection was eradicated in 72%, 88%, and 82% of intention-to-treat group (similar data in per-protocol patients) (Wong et al 2001).

Even a 10-day PPI treatment once daily, coadministered with amoxicillin 1000 mg/bid and clarithromycin 500 mg/bid (the antibiotics for only 5 days) has been proven to heal duodenal ulcers. One hundred and twenty-seven patients were randomized into 3 groups: rabeprazole 20 mg, rabeprazole 40 mg and omeprazole 40 mg. The intention-to-treat analysis evidenced comparable (differences not statistically significant) cure rates between the groups: 85.7% for rabeprazole 20 mg, 90% for rabeprazole 40 mg and 93.3% for omeprazole 40 mg (Catalano et al 2002).

Ando et al (2005) recently demonstrated that healing efficacy of rabeprazole is less influenced by CYP2C19 genetic polymorphism than that of omeprazole and, hence, this attitude can result in an earlier repair of gastric mucosal damage. Eighty patients with active gastric ulcer received rabeprazole 10 mg or omeprazole 20 mg once daily for 8 weeks. The improvement of gastric ulcer size and ulcer healing rates were stratified per CYP2C19 subgroups metabolizers after 2 and 8 weeks of treatment. The mean 2-week posttreatment ulcer size differed significantly between metabolizers in omeprazole group (35.8 ± 45.2 mm^2 vs 14.6 ± 16.2 mm^2 vs 33.9 ± 53.0 mm^2 respectively for homozygous extensive metabolizers, heterozygous extensive metabolizers and poor metabolizers), but not in rabeprazole one (8.4 ± 8.4 mm^2 vs 8.9 ± 9.5 mm^2 vs 18.2 ± 14.7 mm^2), leading to a statistical difference between rabeprazole and omeprazole homozygous extensive metabolizers ($p = 0.0057$). At 8 weeks both PPIs showed similar high healing figures. Even the percentage healing ratios of ulcer areas were more reproducible in rabeprazole group at 2 weeks ($80.7 \pm 17.4\%$ vs $89.3 \pm 12.5\%$ vs $84.3 \pm 13.2\%$, respectively, for homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers), than in omeprazole one ($63.4 \pm 24.6\%$ vs $85.2 \pm 12.2\%$ vs $84.0 \pm 16.4\%$, $p = 0.0347$ rabeprazole vs omeprazole in homozygous extensive metabolizers), resulting in an overall significant difference ($85.9 \pm 14.4\%$ vs $76.5 \pm 21.0\%$, $p = 0.0210$ rabeprazole vs omeprazole total healing rate).

Finally, low-dose rabeprazole could achieve the same ulcer healing rates as full-dose omeprazole in 112 patients with at least one active gastric antral or duodenal ulcer (diameter ≥ 5 mm to ≤ 30 mm) at baseline visit. Patients received rabeprazole 10 mg or omeprazole 20 mg once daily for 6 weeks and were evaluated endoscopically and clinically (symptom severity) at 1 and 6 weeks of treatment. The remaining ratios of peptic ulcers were equivalent in both groups after 1 week of therapy ($45.5 \pm 33.0\%$ vs $50.3 \pm 35.2\%$, $p = 0.475$ rabeprazole vs omeprazole) and at 6 weeks (80.6% vs 87.0%, $p = 0.423$ rabeprazole vs omeprazole). Day pain and night pain severity consistently decreased in both groups at 6 weeks (patients with day pain and night pain resolution were respectively 63.6% and 72.4% in rabeprazole group vs 64.3% and 73.1% in omeprazole one, p = ns) (Ji et al 2006).

Pharmacoeconomics and quality of life

Since GERD is a chronic, relapsing condition with probably the majority of patients requiring long-term maintenance therapy, prescription rates and attendant costs of PPIs continue to rise. The initial choice of treatment has, therefore, long-term cost implications.

A model including medical costs for hospitalizations, procedures, and office visits was developed (Ofman et al 2000) to compare the cost-effectiveness of rabeprazole and ranitidine in acute and maintenance therapy for erosive esophagitis using symptom response, rather than endoscopic healing, as the clinical outcome. The per-patient cost of rabeprazole therapy resulted higher than that of ranitidine therapy (US$2020 vs US$1917), but rabeprazole was more effective in preventing symptomatic recurrences (74% vs 41%). Rabeprazole had also a lower average cost-effectiveness ratio than ranitidine (US$2748 vs US$4719 per symptomatic recurrence prevented). Therefore management of esophagitis with rabeprazole is more effective and may be more cost effective, than with generic ranitidine.

PPI prescriptions might be appropriate or not. In an Irish general hospital (Mat Saad et al 2005), where the 30.6% of inpatients were on PPI therapy, up to one-third of cases had an unapproved or unknown indication, and even if the 70.8% of PPI therapies had been initiated in hospital, only one-third of the patients on PPI therapy had undergone endoscopy. Rabeprazole, the least expensive PPI, was the least prescribed. Of note, the substitution of the PPI with the greatest individual cost with any of the alternative agents, particularly the generics omeprazole preparations, rabeprazole, and pantoprazole, in accordance with therapeutic indication, would be expected to produce important cost savings. Decision analysis was used (Ofman et al 2002) to calculate the clinical and economic outcomes of competing (traditional step-up plus endoscopy vs PPI test plus step-down therapy) management strategies. Based on the results of this analysis, PPI test followed by a "step-down" approach may result in improved symptom relief and quality of life over 1 year, and more appropriate utilization of invasive diagnostic testing at a small marginal increase in total costs.

Savings might be further enhanced by increasing the step-down strategy from healing to maintenance doses of these drugs (McGowan et al 2005).

In order to compare the costs and effectiveness of treatment of not investigated GERD with other available PPIs, even in generic formulations, a treatment model was developed incorporating acute treatment, long-term continuous, or on-demand maintenance therapy and number of endoscopies to confirm diagnosis (Remak et al 2005). Generic omeprazole and rabeprazole cost less and resulted in more symptom-free days and higher quality-adjusted life years (QALY) gains than the other PPIs. Moreover, rabeprazole had a favorable cost-effectiveness ratio of £3.42 per symptom-free day and £8308 per quality-adjusted life-year gained when compared with generic omeprazole, remaining cost-effective independently of choice of continuous vs on-demand treatment.

In another model (Dubois et al 2005) developed for endoscopy-confirmed NERD patients in the UK, on-demand use of rabeprazole incurred the lowest cost in comparison with the other PPIs, with base-case annual median cost and utility gained with on-demand rabeprazole therapy respectively of €123 euro and 0.89. Differences in costs, but not in outcomes, were statistically significant, and the results were robust to sensitivity analyses.

All PPIs that have holding time of intragastric pH >4 for at least 11 hours in 24-hour period; a study has been conducted aiming at correlating cost of therapy with holding-time characteristics of 4 PPIs (esomeprazole, lansoprazole, omeprazole, and rabeprazole) (Kivioja et al 2004). The cost-minimization analysis produced 2 least expensive PPIs, one in the range of 11 hours or more of holding time and one in the range of 12 hours or more, which were respectively lansoprazole (average cost of €138.89 per patient) and rabeprazole (€193.81 per patient).

A large study conducted on 75,452 newly diagnosed GERD subjects (Hall et al 2002) revealed 67.9% of subjects treated with lansoprazole, 30.3% treated with omeprazole, and only 1.8% under rabeprazole treatment. In this cohort rabeprazole subjects had lower GERD-related costs, less escalation to higher drug dosages, and fewer tablets consumed per day, compared with lansoprazole and omeprazole subjects. Compliance was not significantly different between the drugs, and increased compliance did not decrease GERD-related costs.

In 2000 Farley et al (2000) compared rabeprazole and the histamine H_2-receptor antagonist ranitidine in the treatment of erosive gastroesophageal reflux disease. Patients were randomized to rabeprazole 20 mg daily or to ranitidine 150 mg 4 times daily, and evaluated for heartburn symptoms, overall sense of wellbeing, time lost from daily activities, antacid use, and adverse events. At weeks 4 and 8 there were significant differences favoring rabeprazole with respect to resolution or improvement of heartburn symptoms and improvement in sense of wellbeing, which can be considered a non-specific form of quality of life measurement.

Johanson et al (2002) assessed the effect of rabeprazole 20 mg once a day on quality of life of refluxers participating in an open-label, 8-week, study, as measured with the SF-36 Health Survey. All SF-36 scales mean scores improved significantly ($p \leq 0.007$) from baseline to week 8. All the improvements were also clinically meaningful, except for physical functioning, general health and mental health.

Rabeprazole treatment normalized baseline scores in role limitations due to physical problems, social functioning, role limitations due to emotional problems, and mental health that were significantly poorer than those of the general population at the beginning of the study.

To determine the influence of *H. pylori* infection on effectiveness of rabeprazole in primary and secondary care, Wit et al (2004) tested for *H. pylori* 1787 patients from primary and secondary care centers with uninvestigated suspected GERD (based on symptoms only) and investigated GERD (endoscopically confirmed oesophagitis or endoscopy-negative reflux disease) and then treated them with rabeprazole 20 mg once daily for 4–8 weeks in a non-randomized, multicenter, open-label study. Resolution of both heartburn and acid regurgitation was evaluated at 4 and 8 weeks, as well as quality of life as registred with the Psychological General Well-being Index. Mean duration of treatment was 36.3 days. At the re-evaluation visit 76.9% were heartburn-free, 77.7% regurgitation-free, and 71% had complete symptom resolution. Overall Psychological General Well-being Index scores improved accordingly. Treatment was equally effective in patients with or without *H. pylori* infection, but more effective in patients with esophagitis when compared with non-erosive GERD.

Possible new indications

A mechanism of tumor resistance to chemotherapy may be the alteration of the tumor microenvironment via changes in the pH gradient between the extracellular environment and the cell cytoplasm (De Milito and Fais 2005), impairing the uptake of weakly basic chemotherapeutic drugs, and reducing their effect. An option to revert multi-drug resistance could be to target the vacuolar H^+-ATPases (V-H^+-ATPases) that pump protons across the plasma membrane. Rabeprazole directly inhibits V-H^+-ATPases and PPI pretreatment sensitizes tumour cell lines to the effect of cisplatin, 5-fluorouracil and vinblastine. PPI pretreatment was associated with the inhibition of V-H^+-ATPases activity and an increase of both extracellular pH and the pH of lysosomal organelles, consistent with a cytoplasmic retention of the cytotoxic drugs and targeting to the nucleus in the case of doxorubicin. An in vitro study (Itagaki et al 2004) revealed that extremely high concentrations of rabeprazole increase rhodamine 123 uptake via MDR1 between 68% and 185% in Caco-2, HeLa and Hvr100-6. At the levels observed in plasma (approximately 1 μM), the drug interaction with MDR1 should be minimal in patients under rabeprazole treatment.

The substituted benzimidazoles omeprazole, lansoprazole, rabeprazole, and pantoprazole were also found to have in vitro activity against three different isolates of *Plasmodium falciparum* (Riel et al 2002), some of which are chloroquine and pyrimethamine resistant or multidrug resistant. Lansoprazole and rabeprazole were the most effective. Further studies are needed to ascertain if there is a clinical correlate of these in vitro properties.

Notes

Data selection

Sources: Medical literature published in English up to spring 2006 since January 2001 (included) concerning clinical studies, and since January 1999 concerning pharmacological studies, conducted with rabeprazole, identified using Medline and EMBASE.

Selection: studies in patients with acid-related disorders, primarily GERD and peptic ulcer, who received rabeprazole. Relevant pharmacodynamic and pharmacokinetic data are also included.

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