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Alimentary Tract

Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease
A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole

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Abstract

Background. Previous studies have shown similar effects of rabeprazole and omeprazole, when used at the same dose in the treatment of reflux oesophagitis. However, such studies have been conducted as superiority studies but interpreted as equivalence ones.

Aim. To properly assess the comparative efficacy of rabeprazole and omeprazole in inducing complete endoscopic healing and symptom relief in patients with reflux oesophagitis.

Methods. Patients ($n = 560$) with Savary–Miller grade I–III reflux oesophagitis were randomised in a double-blind, double-dummy fashion to rabeprazole or omeprazole 20 mg once daily for 4–8 weeks. Then, patients endoscopically healed and symptomatically relieved were openly maintained with rabeprazole 10 mg or 2×10 mg once daily (in the event of clinical and/or endoscopic relapse) for a maximum of 48 weeks.

Results. After 4–8 weeks of treatment, healing (primary end-point) was observed in 228/233 (97.9%) patients in the rabeprazole group and in 231/237 (97.5%) in the omeprazole one (equivalence effect demonstrated by $p < 0.0001$ at Blackwelder test and an upper confidence limit at 97.5% of 0.023). However, rabeprazole was faster in inducing heartburn relief than omeprazole (2.8 ± 0.2 versus 4.7 ± 0.5 days of therapy to reach the first day with satisfactory heartburn relief, $p = 0.0045$ at log-rank test). In the maintenance phase, 15.2% of patients had an endoscopic and/or clinical relapse.

Conclusion. Rabeprazole is equivalent to omeprazole in healing reflux oesophagitis, but shows a faster activity on reflux symptoms in the early treatment phase.
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Keywords: Curative/maintenance therapy; Gastro-oesophageal reflux disease; Heartburn; Rabeprazole

1. Introduction

Gastro-oesophageal reflux disease (GORD) is a highly prevalent gastrointestinal disorder and is one of the most common gastroenterological illnesses encountered in clinical

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practice, affecting all age groups, particularly older adults [1]. As an example, a cross-sectional survey conducted in the USA in 1976 among healthy adults found that 7% of individuals experienced heartburn daily, 14% weekly and 15% monthly [2]. More recently, two surveys conducted in the USA and the UK show that approximately 20% of the general adult population experiences heartburn at least once weekly [3,4].

GORD has a significant negative impact on health-related quality of life (HRQoL) [5,6] comparable to that induced by clinically relevant diseases such as angina pectoris or mild heart failure [7]. Interestingly, HRQoL impairment due to GORD is more related to the severity of symptoms than to the presence or absence of mucosal lesions, and can be fully restored with effective therapy [8]. Finally, the disease has a tendency to persist for years or even decades [9], i.e., it is not a self-limiting one and a maintenance therapy is needed in the majority of patients.

The goals of treatment are, therefore, two-fold: to relieve symptoms and heal mucosal lesions, if present, and to prevent relapses, which occur almost inevitably after acute treatment discontinuation [8]. Proton pump inhibitors (PPIs) are at present the best therapeutic choice for achieving all these goals; on one hand, they have been shown to be superior to H_2-receptor antagonists in acutely healing erosive/ulcerative lesions and relieving symptoms [10,11], on the other hand, maintenance treatment with such drugs appear to be an effective and appropriate form of therapy in many GORD patients and it is recommended in current practice guidelines [1].

Rabeprazole is a recently introduced PPI, shown to be highly effective. When compared with placebo or ranitidine, rabeprazole achieved significantly higher healing rates and symptom relief [12,13]. Moreover, previous studies have already shown the similar efficacy with omeprazole, in both short- and long-term therapy of GORD [14–17]. However, these studies are potentially biased since they have been originally planned as superiority-studies but interpreted a posteriori as equivalency ones as long as they were not able to detect any differences between the two PPIs. This way of demonstrating absence of therapeutical differences has recently been claimed not only to be poorly supported by the evidence, but also inherently wrong from a statistical point of view [18]. As a matter of fact, trials to assess equivalence need rigorous methods, such as appropriate statistical design and tests [19]. The primary aim of the present study was to assess, by an ad hoc design and analysis, the equivalent comparative efficacy of rabeprazole and omeprazole at standard doses (20 mg once daily) in inducing complete healing of mucosal damage in patients with reflux oesophagitis of grades I–III according to the Savary–Miller classification and reflux symptoms of intensity $\geq$2 on a Likert scale from 0 to 5.

Secondary aims were (i) to assess the efficacy of low-dose (10 mg once daily) rabeprazole in maintaining symptomatic and endoscopic remission for 1 year with a flexible therapeutic approach, i.e., treating healed patients with a low dose and, in case of symptomatic/endoscopic relapse, returning to full dose until the end of the year; (ii) to evaluate the time of action of rabeprazole 20 mg once daily and omeprazole 20 mg once daily in inducing symptom relief in the curative phase of the trial; (iii) to evaluate the impact of curative treatments and initial grading of oesophagitis on the outcome of the maintenance treatment.

2. Materials and methods

2.1. Study design

The study was conducted at 71 Italian investigational sites (see Appendix). It was divided into two phases; after giving their written informed consent, patients with moderate to very severe reflux symptoms and endoscopic evidence of mild to severe oesophagitis entered a curative phase where they were randomised in a double-blind, double-dummy fashion, to either rabeprazole 20 mg or omeprazole 20 mg daily for at least 4 weeks. During this phase, patients were invited to take before breakfast, in a double-blind, double-dummy way, one tablet of rabeprazole 20 mg + one omeprazole-placebo capsule once daily or vice versa, i.e., one capsule of omeprazole 20 mg + one rabeprazole-placebo tablet. Randomisation to treatments was done centrally by means of a randomisation list. Those patients who were not endoscopically cured and not symptomatically improved after 1 month received the curative treatment for an additional 4 weeks. Control visits were repeated every 2 weeks. At the end of the first phase, patients with improvement in reflux symptoms and complete endoscopic healing were admitted to an open, long-term maintenance period with a low dose (10 mg once daily) of rabeprazole for a maximum duration of 48 weeks. In this phase, patients received in an open way one tablet of rabeprazole 10 mg once daily in the morning. The dosage was to be doubled to 2 × 10 mg rabeprazole tablets once daily until the end of the study in case of clinical and/or endoscopic relapse.

During this phase, control visits were performed every 12 weeks, but extra visits were foreseen whenever the patients required them for efficacy and tolerability problems.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions and with Good Clinical Practice (GCP). The study protocol was approved by the appropriate Independent Ethics Committees.

2.2. Patients

Main inclusion criteria for the curative phase were (i) male and/or female outpatients aged $\geq$18 years; (ii) presence of oesophagitis of grades I–III (according to the four-degree Savary–Miller classification) at an endoscopy during the last 7 days prior to inclusion in the trial; (iii) a minimum heartburn score of 2 (see assessment) for both frequency and intensity at daytime and/or nighttime; (iv) a history of at least 3 months

of oesophagitis-like symptoms and heartburn for at least 3 days in each of the 2 weeks prior to inclusion.

Inclusion criteria for the maintenance phase were (i) complete healing of oesophagitis confirmed by endoscopy at the end of the curative phase; (ii) relief of reflux symptoms, defined as a score ≤1 for both frequency and intensity of daytime and nighttime heartburn.

Main exclusion criteria were (i) oesophagitis of infectious origin or caused by exogenous acid or alkaline substances; (ii) grade IV oesophagitis according to Savary–Miller; (iii) Zollinger–Ellison syndrome; (iv) presence of an active gastroduodenal ulcer or previous oesophageal, gastric or biliary surgery (including vagotomy); (v) primary oesophageal motility disorders; (vi) recent treatment with PPIs (within 2 weeks) and previous (for more than five consecutive days in the 2 weeks prior to trial entry) or concomitant therapy with H_2-receptor antagonists, prokinetic agents, anticholinergics or mucosal protective agents; (vii) pregnancy or breast-feeding female; (viii) severe liver and/or renal disease, end-stage heart or lung disease; (ix) cancer or HIV infection; (x) daily use of NSAIDs; alcoholism or drug abuse.

2.3. Assessments

2.3.1. Endoscopy

An endoscopy was performed at the baseline visit, after 4 weeks of double-blind treatment and after 8 weeks if no endoscopic healing was seen at 4 weeks. Moreover, patients had a final evaluation at 48 weeks of the maintenance phase, but an additional endoscopy could be performed whenever the investigator judged it necessary.

The scoring according to the Savary–Miller scale was as follows: grade I, one or more non-confluent erosions; grade II, confluent mucosal erosions which did not involve the entire circumference of the oesophageal lumen; grade III, confluent erosions which involved the entire circumference of the oesophageal lumen; grade IV, ulcer, stricture, short oesophagus and/or Barrett's oesophagus.

Helicobacter pylori status was assessed by histology (at least two biopsies from the antrum and two biopsies from the body of the stomach) at the time of baseline endoscopy.

2.3.2. Reflux symptoms

Reflux symptoms such as regurgitation, daytime and nighttime heartburn and other associated complaints (epigastric pain/burning, dysphagia, nausea, nocturnal coughing and nocturnal wheezing) were assessed by the investigator at baseline and at every visit until the end of the study, using the following scoring system and referring to the week prior to the visit.

Intensity: 0 = absent; 1 = mild (present, but causing little or no discomfort); 2 = moderate (annoying, but not interfering with usual activities or with sleep); 3 = severe (causing marked discomfort and some interference with usual activities or with sleep); 4 = terrible (disabling, considerable interference with usual activities or sleep).

Frequency: 0 = absent; 1 = occasional (≤2 days/week); 2 = frequent (3–4 days/week); 3 = very frequent (5–6 days/week); 4 = every day (7 days/week).

Patients were asked to keep a daily diary to record the intensity of reflux symptoms throughout the curative phase with the same scoring system described above.

2.3.3. Overall assessment and global evaluation

At each visit of the trial after the baseline evaluation, patients were also queried on their condition (reflux symptoms and general well-being), rating it on the following five-point Likert scale: 0 (very good), 1 (good), 2 (fair), 3 (poor) and 4 (very poor).

Data were also collected on the use of rescue (antacid) medication and adverse events.

2.4. Statistical analysis

The primary endpoint of the study was to confirm the equivalence of the two drugs on the endoscopic healing rate at the end of the curative phase, i.e., after 4–8 weeks of double-blind treatment in the per-protocol patient sample.

The sample size was calculated assuming a response rate (endoscopic cure of oesophagitis) with rabeprazole 20 mg once daily or omeprazole 20 mg once daily of 88%; under these circumstances, a number of 222 patients in each treatment group were required to be able to detect a 10% difference between treatments with an alpha value of 2.5% and a power of 90%. Considering a 10% rate of incomplete, missing or drop-out data, it was estimated to have a sample of 504 patients.

The Blackwelder test was used to prove equivalence of rabeprazole versus omeprazole with an allowable clinical difference of 10%. According to this test, the equivalence between two drugs is shown by a p-value ≤0.05 and the upper confidence limit, calculated at 97.5%, should be included in the above allowable clinical difference of 10% (range 0–0.1). Thus, contrary to the superiority trials, where a p-value ≤0.05 is synonymous with proven statistical difference between two drugs, in equivalency ones such as ours, a p-value of a Blackwelder test ≤0.05 means statistically proven equivalence [20].

Secondary endpoints were (1) time to onset of relief of heartburn (intensity ≤1) and (2) time to complete relief of heartburn (intensity = 0) in the curative phase, during both daytime and nighttime together or separately, respectively; (3) percentage of patients with satisfactory relief of heartburn (daytime and nighttime intensity ≤1) and (4) percentage of patients with complete relief of heartburn (daytime and nighttime intensity = 0) in each day of the first 3 and 7 days of the curative phase, during both daytime and nighttime together or separately, respectively; (5) time to clinical/endoscopic relapse during the maintenance phase; and (6) overall assessment and global evaluation. For analysis of secondary endpoints, the intention-to-treat (ITT) population was considered. However, the occurrence of the

endoscopic/clinical relapse in the maintenance phase was evaluated with a per-protocol analysis of those patients who completed the trial and for whom it was possible to collect the efficacy parameters.

Time to relief of heartburn and time to clinical and/or endoscopic relapse were evaluated by means of log-rank test. The percentage of patients with satisfactory/complete relief of heartburn, the overall assessment and the global evaluation were analysed by means of Cochran–Mantel–Haenszel statistics.

Adverse events were analysed in the safety sample, which included all randomised patients who received at least one dose of the study medication.

3. Results

3.1. Patients

Overall, 560 patients were included in the curative phase (an average of 7.9 patients enrolled per centre, ranging between a minimum of one and a maximum contribution of 19 patients) and were randomised, 283 in the rabeprazole group and 277 in the omeprazole group. Of the enrolled patients, 513 completed the first phase and 47 patients (25 in the rabeprazole group and 22 in the omeprazole group) dropped out due to different reasons. As far as the maintenance phase is concerned, 502 patients were admitted, 253 from the rabeprazole group and 249 from the omeprazole group: out of these patients, 425 completed the maintenance study, while 77 patients (44 from the rabeprazole group and 33 from the omeprazole group) left the study prematurely.

The flow of patients through the two phases of the study, according to the CONSORT guidelines, is shown in Fig. 1.

Patient demographic and baseline characteristics were well matched amongst the two treatment groups (Table 1).

3.2. Efficacy curative phase

3.2.1. Endoscopic healing

After 4 weeks of treatment, 212/233 patients (91.0%) in the rabeprazole group and 213/237 (89.9%) in the omeprazole group were completely healed ($p < 0.0001$ at Blackwelder's test and an upper confidence limit at 97.5% of 0.042).

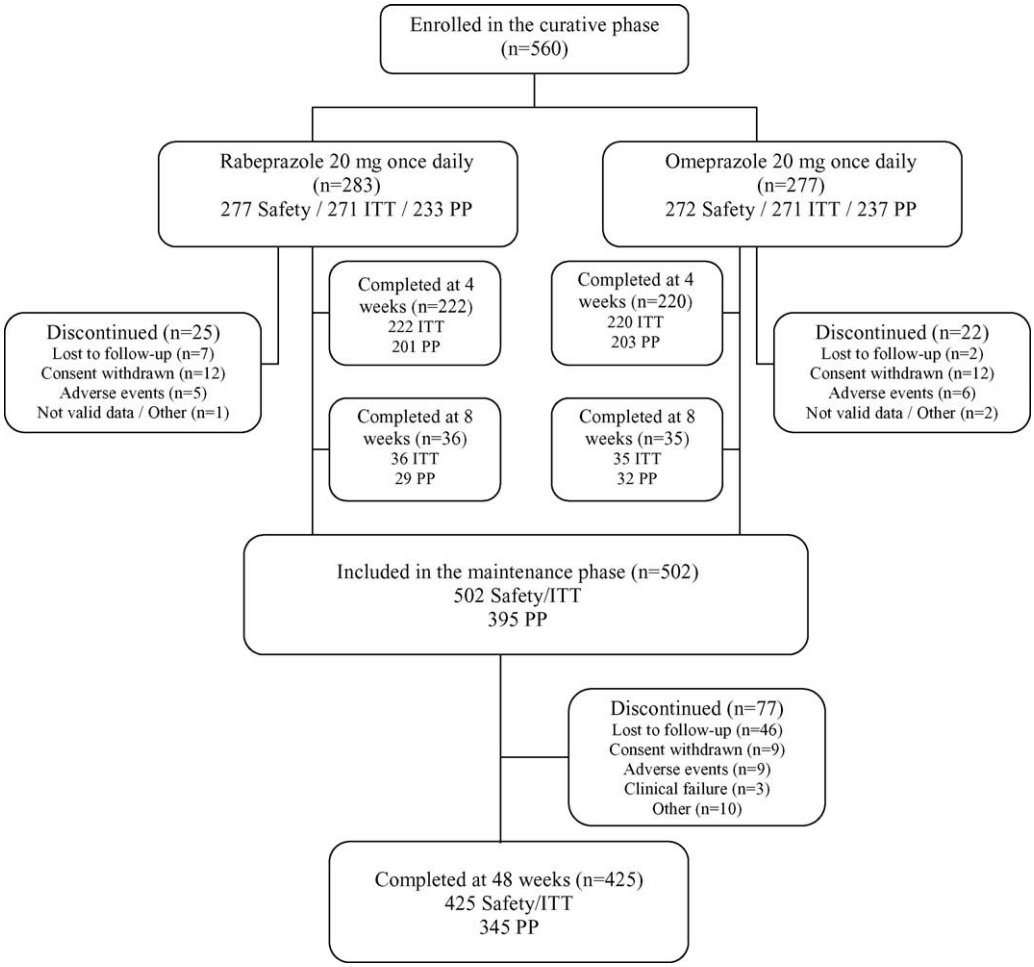

Fig. 1. Randomisation protocol and patient disposition.

Table 1
Baseline demographic and clinical characteristics of patients (safety patients, $n = 549$)

	Rabeprazole ($N = 277$)	Omeprazole ($N = 272$)
Gender (*n*, %)		
Male	190 (68.6%)	184 (67.7%)
Female	87 (31.4%)	88 (32.3%)
Age (years), mean (±S.D.)	47.7 (±14.2)	47.1 (±14.9)
Body mass index (BMI) (kg/m^2), mean (±S.D.)	26.2 (±3.6)	26.6 (±3.8)
Duration of symptoms (months), mean (±S.D.)	51.5 (±59.0)	56.6 (±67.2)
Patients with a first episode of oesophagitis (*n*, %)	186 (67.2%)	200 (73.5%)
Oesophagitis grade (*n*, %)		
Grade 0	3 (1.1%)	3 (1.1%)
Grade I	188 (67.9%)	192 (70.6%)
Grade II	71 (25.6%)	62 (22.8%)
Grade III	15 (5.4%)	15 (5.5%)
Regurgitation (*n*, %)	231 (83.4%)	219 (80.5%)
Heartburn (*n*, %)		
During daytime	272 (98.2%)	265 (97.4%)
During nighttime	206 (74.4%)	205 (75.4%)
Epigastric pain (*n*, %)	196 (70.8%)	190 (69.9%)

Endoscopic lesions after 4 more weeks of treatment were still evident in two out of 21 patients (both grade I) in the rabeprazole group and in five out of 24 patients (four grade I and one grade II) in the omeprazole group, bringing the success rate at endpoint to 97.9% (228 of 233) in the rabeprazole group and 97.5% (231 of 237) in the omeprazole group ($p < 0.0001$ at Blackwelder's test and an upper confidence limit at 97.5% of 0.023) (Fig. 2). The healing rate at endpoint in the two groups, according to the initial grade of oesophagitis, is presented in Fig. 3. Again, no differences can be seen between the two groups, even if a numerical trend is present in favour of rabeprazole in the most severe grade.

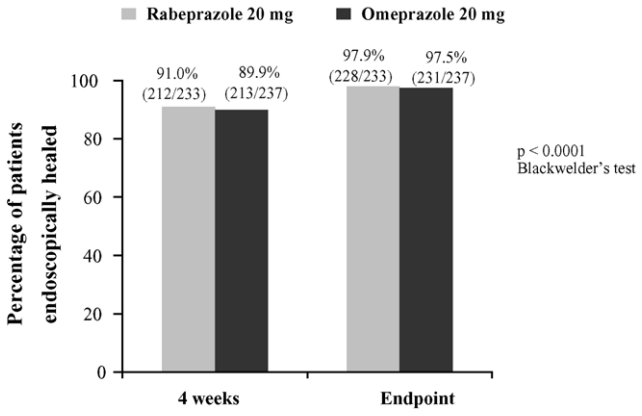

Fig. 2. Healing rates at 4 weeks and at endpoint according to treatment (per-protocol patients) (rabeprazole $n = 233$, omeprazole $n = 237$). Please note that $p < 0.0001$ at Blackwelder's test means that the equivalence between the two drugs is statistically significant (cf. Section 2.4 in the text).

3.2.2. *Reflux symptoms*

In the ITT population, the mean time to the first day with satisfactory heartburn relief was significantly shorter for the rabeprazole group patients ($n = 271$) (2.8 ± 0.2 days, mean ± S.E.M.) than with the omeprazole group patients ($n = 271$) (4.7 ± 0.5 days) ($p = 0.0045$ at log-rank test).

Mean time to complete heartburn relief was similar: 7.2 days in the rabeprazole group ($n = 271$) and 8.4 in the omeprazole group ($n = 271$) ($p = 0.1342$ at log-rank test).

Rabeprazole also showed a more sustained activity compared with omeprazole in controlling reflux symptoms in each day of the first week of the curative phase: 32.2% (79 of 245) of patients in the rabeprazole group reported complete

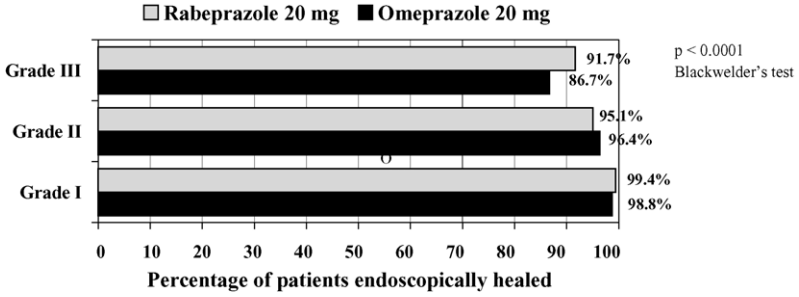

Fig. 3. Healing rates according to initial oesophagitis grade and treatment (per-protocol patients) (rabeprazole $n = 233$, omeprazole $n = 237$). Please note that $p < 0.0001$ at Blackwelder's test means that the equivalence between the two drugs is statistically significant (cf. Section 2.4 in the text).

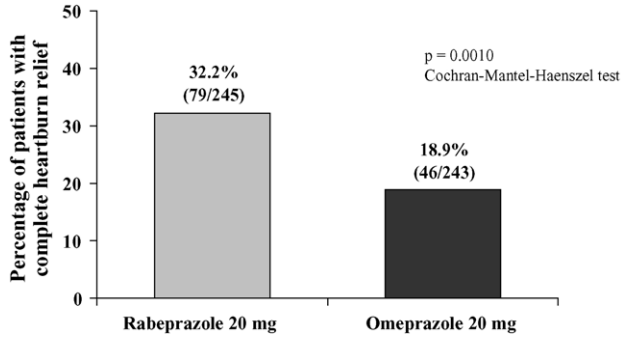

Fig. 4. Percentages of patients with complete heartburn relief (daytime and nighttime) in each day of the first week of treatment (ITT patients) (rabeprazole n =245, omeprazole n = 243).

heartburn relief during both daytime and nighttime compared with 18.9% (46 of 243) in the omeprazole group (p = 0.0010, at Cochran–Mantel–Haenszel test) (Fig. 4), whereas the percentage of patients with satisfactory heartburn relief during the same period was 50.6% (124 of 245) and 41.2% (100 of 243), respectively (p = 0.0585, at Cochran–Mantel–Haenszel test).

Interestingly, the effect of both treatments was more pronounced on the nighttime symptoms than on the daytime ones. Complete relief of nighttime heartburn was observed, after 7 days of therapy in 53.9% (132 of 245) patients in the rabeprazole group and in 42.8% (104 of 243) patients in the omeprazole group (p = 0.0195), but only in 83 out of 245 (33.9%) and 66 out of 243 (27.2%), respectively, during the daytime (p = 0.1224) (Fig. 5). The same trend was observed when analysing the first 3 days of treatment; daytime and nighttime heartburn were completely relieved in 37.1% (91 of 245) of rabeprazole group versus 23.1% (56 of 243) of omeprazole one (p = 0.0008). Again, the effect was more evident for nighttime symptom, 60.0% (147 of 245) versus 48.2% (117 of 243) (p = 0.0143).

3.2.3. Overall assessment and global evaluation

Patients' assessment changed similarly for the two groups from baseline visit to endpoint visit. The percentage of patients scoring their overall assessment for reflux symptoms as very good or good increased from 7.0 (rabeprazole group) and 5.5% (omeprazole group) to 90.0 and 90.7%, respectively, at the end of the acute phase. As far as general well-being is concerned, the figures were slightly lower at the end of the curative phase, changing from 41.7 (rabeprazole group) and 43.5% (omeprazole group) at the baseline to 89.3 and 86.3% at the end of this phase.

3.2.4. Antacid consumption

Ten percent of patients in the rabeprazole group and 13.6% in the omeprazole group reported use of antacids at the first visit after the baseline. This percentage decreased to less than 7% in both groups at the endpoint. The data were not statistically different.

3.2.5. Efficacy maintenance phase

In the ITT sample an endoscopic relapse was observed in 44 out of 422 valuable patients (10.4%) for this parameter; interestingly, in all the cases, endoscopic relapse was fully asymptomatic. A clinical relapse occurred in 39 out of 475 valuable patients (8.2%) for this parameter; grouping together those who had endoscopic and/or clinical relapse brought the total up to 15.2% (n = 73/480) of patients. The time to occurrence was 11.1 ± 2.6 months for endoscopic relapse, 7.7 ± 4.4 for clinical relapse and 9.5 ± 3.9 for endoscopic and/or clinical relapse.

There was no statistically significant influence on relapse at the log-rank test by using as covariate initial grading and/or curative treatment, age, gender or BMI.

The percentage of patients that gave a favourable judgement (very good + good) of the overall assessment decreased in relation to the time to the clinical/endoscopic relapse, from 88.6% at 12 weeks to 75.9% at 48 weeks for reflux

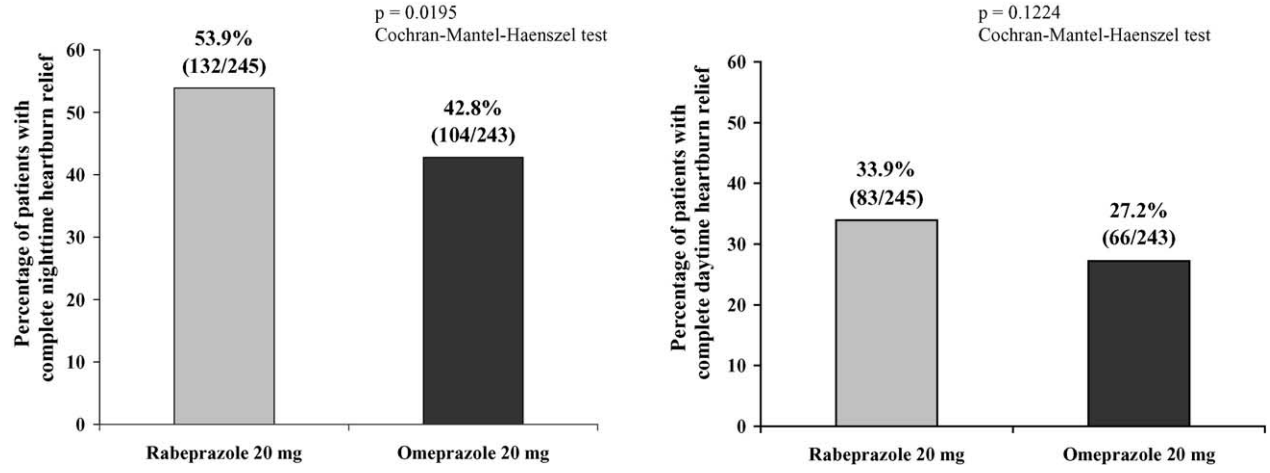

Fig. 5. Percentages of patients with complete heartburn (nighttime left panel, daytime right panel) relief in each day of the first week of treatment (ITT patients) (rabeprazole n = 245, omeprazole n = 243).

symptoms, and from 87.7 to 76.7% for general well-being, respectively.

Antacid consumption throughout the maintenance phase was reported on average by less than 5% of patients.

Finally, in 32 out of 38 per-protocol patients showing an endoscopic relapse, the oesophagitis was found at the final examination in the complete absence of any preceding symptom. In six out of 38 patients, who relapsed during the maintenance phase, a double dose of rabeprazole was able to induce endoscopic healing in half of them within 4–8 weeks.

With regard to symptom response, only 14 out of 395 per-protocol patients, who completed the trial, still complained of relevant symptoms (defined as frequency and intensity of daytime and nighttime heartburn ≥ 2).

3.2.6. H. pylori status

No effect was observed as far as the influence of the *H. pylori* status at baseline on the primary efficacy variable is concerned. Grouping together the patients of the two treatment arms, at the end of the curative phase healing occurred in 168 out of 171 (98.2%) *H. pylori* +ve subjects as compared to 276 out of 284 (97.2%) *H. pylori* −ve patients, (odds ratio 1.6232; CI 0.4247–6.2033), whereas reflux symptoms relief (defined as frequency and intensity of daytime and nighttime heartburn ≤ 1) was reported in 167 out of 171 (97.7%) *H. pylori* +ve subjects as compared to 276 out of 284 (97.2%) *H. pylori* −ve patients (odds ratio 1.2101, CI 0.3589–4.0806).

In the maintenance phase, a clinical and/or endoscopic relapse occurred in 15 of 144 (10.4%) *H. pylori* +ve subjects as compared to 37 of 242 (15.3%) *H. pylori* −ve patients (odds ratio 1.5522, CI 0.8192–2.9410).

3.2.7. Analysis of adverse events

Two percent of patients were withdrawn from the study due to adverse effects during the acute phase and 1.8% during the maintenance period. Overall, the percentage rate of adverse events remained stable or even decreased from the acute to the maintenance phase.

The most frequent adverse events were recorded on the GI system. There was no significant difference between treatment groups in single adverse events occurring during the acute phase, with the sole exception of headache; it was reported more frequently in the omeprazole than in the rabeprazole group (4.8% $n = 13/17$ versus 1.4% $n = 4/17$, $p = 0.0241$, at the Chi-square test). The treatment-related adverse events were similar to those already known from international literature and product characteristic summaries for test and reference drugs. Serious adverse effects in the curative phase occurred in only three patients, all belonging to the omeprazole group, but were not related to omeprazole therapy in itself in all instances.

Concerning the maintenance phase, severe adverse effects occurred in 12 patients. There was no adverse event with an incidence greater than 2%, and only few events with an incidence greater or equal to 1%, such as flu (1.8%), fever (1.0%), hypertension (1.0%), headache (1.8%), dyspepsia (1.2%), diarrhoea (1.2%), sciatalgia (1.4%) and abdominal pain (1.2%).

4. Discussion

This study confirms the overall equivalence of the two treatments, rabeprazole and omeprazole, on acute healing of reflux oesophagitis by adopting a statistically appropriate method; at the same time, the clinical results underline the faster and more sustained activity of rabeprazole on reflux symptoms in the early treatment phase.

Rabeprazole has already been shown to be equivalent to omeprazole, when used at the same dose (20 mg daily), in inducing healing of endoscopic oesophagitis [14,15]. Moreover, when compared with double dose of omeprazole (40 mg daily), rabeprazole at the standard 20 mg daily showed to be equivalent to the former in inducing endoscopic healing at 4–8 weeks and in relieving heartburn [16]. These studies, however, may be criticised because they are in essence superiority studies, but as they fail to show any significant difference, they are a posteriori interpreted as if they would have been planned and executed as equivalence ones.

We planned already from the design (calculation of sample size, choice of statistical tests) to perform our study as a true equivalence one [19]. By doing so, and in particular by adopting the Blackwelder test for the equivalence, we can truly say that healing rates observed with the two drugs are equivalent, either at 4 weeks (91.0% healed with rabeprazole versus 89.9% with omeprazole) or at the endpoint (97.9% versus 97.5%, respectively). The reason for this considerably high healing rate in either group is probably to be accounted by the high proportion of patients (roughly two-thirds) with grade 1 oesophagitis at baseline, which is known to show the fastest healing rate. Even if the results of endoscopic cure are analysed by initial grade, the data show equivalent results between rabeprazole- and omeprazole-treated patients.

Interestingly, in the above-cited study comparing standard rabeprazole versus double dose of omeprazole [16], significantly fewer patients reported severe heartburn during the first 3 days of treatment in the rabeprazole group, thus suggesting a faster onset of antisecretory action with this drug than with omeprazole.

A faster onset of action of rabeprazole in comparison to other PPIs was demonstrated recently by the study of Pantoflickova et al. [21], who performed a double-blind, randomised, cross-over comparison of rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and omeprazole 20 mg once daily in 18 healthy *H. pylori*-negative subjects. The authors showed that already after 1 day of dosing, intragastric pH and the time with intragastric pH >4 were significantly greater with rabeprazole than with any other PPI investigated.

This favourable pharmacological characteristic of rabeprazole may be clinically translated into a more rapid onset of symptom relief. This was the case in a recent study by Robinson et al. [22] evaluating timing of symptom relief,

changes in symptom severity, HRQoL and safety of rabeprazole therapy in endoscopically confirmed erosive GORD. In this large community-based study, called the Future of Acid Suppression Therapy (FAST) trial, rabeprazole was able to induce substantial symptom relief already on day 1, with continuous improvement over the first week.

In our trial, the mean time to onset and complete relief of symptoms, as assessed by survival analysis, was shorter with rabeprazole than with omeprazole. Also, during the first week of treatment, a significantly higher percentage of patients treated with rabeprazole reported complete relief of symptoms and complete relief of nighttime heartburn than in the group treated with omeprazole.

This finding has several implications for the management of GORD. During the few last years, the role of endoscopy in staging of disease and tailoring of therapy has progressively been reduced [23]. However, modern treatment of GORD, based on potent, safe acid inhibition with PPIs, is "symptom-driven"; the main goal of treatment is the complete relief of symptoms and the restoration of a normal HRQoL, rather than the endoscopically verified complete disappearance of mucosal damage, if present [24]. Even more symptom-driven nowadays is maintenance treatment, largely based on PPI "on-demand" therapy [25], i.e., courses of treatment which can be started and stopped by the patient him/herself according to episodic bursts of symptoms. In this respect, an ideal PPI drug should on one hand achieve an effective control of intragastric, and hence intra-oesophageal pH, since the degree of acid suppression in patients with GORD has been shown to correlate with relief of symptoms and healing rates of oesophagitis [26,27]. On the other hand, it should also provide fast, sustained relief of reflux symptoms as early as possible, since this reinforces the correctness of diagnosis as well as the patient–doctor relationship, and restores quality of life and general well-being.

Due to the different pharmacokinetic characteristics of the different PPIs available, these agents may differ in their onset of symptom relief. This characteristic is, therefore, currently considered of the utmost clinical importance and several studies describing it have appeared in the literature [28,29].

Rabeprazole has shown to provide more rapid and greater acid control than lansoprazole, pantoprazole and omeprazole [17,30], and possibly also than esomeprazole, the S-chiral isomer of omeprazole recently marketed, when used at "equiponderal" doses, i.e., 20 mg versus 20 mg [31].

We believe that, from a clinical point of view, a valuable feature of our study lies in the measurement of the percentages of patients who were completely heartburn-free (i.e., who did not report a single episode of heartburn during the treatment period). Using this rigorous outcome parameter, our findings confirm that rabeprazole not only provides a higher percentage of patients with complete relief of symptoms already during the first 3 days of treatment, but also that it maintains its significantly higher efficacy as compared to omeprazole throughout the first week of therapy. Expressed in terms of number needed to treat (NNT), the superiority of rabeprazole in our study could be better appreciated by considering that the NNT of rabeprazole versus omeprazole in inducing complete daytime and nighttime heartburn relief is 7.5, which is extremely good.

As far as maintenance therapy is concerned, the evidence on the effects of rabeprazole at the time we started the study was preliminary; a study was published on this issue, suggesting the equivalence of 10 and 20 mg once daily in preventing relapse of erosive or ulcerative GORD [32]. Immediately after the publication of this paper, a second study appeared showing the equivalence of rabeprazole 10 mg daily and omeprazole 20 mg daily, when administered for 12 months, in tolerability and in preventing relapse of healed reflux oesophagitis [33]. In this study, the relapse rates were 5 and 4%, respectively, at week 52.

In our study, overall endoscopic and/or clinical relapse was evident in 15.2% of patients after an average 11.1 months of treatment with rabeprazole in the open-label maintenance phase with low dose of the compound, namely 10 mg once daily. This rate is lower than that observed in the study by Birbara et al. [32], i.e., 23% at week 52, and slightly higher than in the study by Thjodleifsson et al. [33].

In conclusion, we have shown, in a large randomised, double-blind, controlled clinical trial, the equivalence of equiponderal doses of rabeprazole and omeprazole in inducing acute healing of reflux oesophagitis. The former drug appears to allow a faster and more sustained onset of action in symptom relief and is safe and effective in maintaining absence of oesophagitis and reflux symptoms when used low-dose. In our study, within 1 year after acute healing the relapse rate with rabeprazole 10 mg daily was 15.2% which is lower than would have been expected from previous studies of similar disease.

Conflict of interest statement

None declared.

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