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Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months

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SUMMARY

Background: Most patients with gastro-oesophageal reflux disease (GERD), regardless of endoscopic status, suffer symptomatic relapse within 6 months of stopping acid suppressant therapy.

Aim: To assess the efficacy of 'on-demand' treatment of GERD with esomeprazole, the first proton pump inhibitor developed as an optical isomer.

Methods: In this multicentre, double-blind study, 342 endoscopy-negative GERD patients demonstrating complete resolution of heartburn during the final week of a 4-week treatment period with esomeprazole 20 mg or omeprazole 20 mg once daily were randomized to receive esomeprazole 20 mg or placebo on demand (maximum of one dose per day) for a further 6 months. Use of rescue antacids was permitted.

Results: All 342 patients (191 males), aged 19–79 (mean 49) years, were evaluable in the intention-to-treat analysis. The proportion of patients who discontinued treatment due to insufficient control of heartburn was significantly higher among placebo compared to esomeprazole recipients (51% vs. 14%; $P < 0.0001$). Patients randomized to esomeprazole on-demand therapy remained in the study longer than those in the placebo group (mean 165 vs. 119 days). Over 50% took the study medication for periods of 1–3 consecutive days (esomeprazole) or 4–13 consecutive days (placebo). Use of antacids was > 2-fold higher among placebo recipients. The frequency of adverse events was similar in the two groups, when adjusted for time spent in the study, as were the clinical laboratory profiles.

Conclusions: On-demand therapy with esomeprazole 20 mg is effective and well tolerated in maintaining symptom control in endoscopy-negative GERD.

INTRODUCTION

The primary goals of therapy for the majority of patients with gastro-oesophageal reflux disease (GERD) are symptom relief and prevention of relapse, while healing is also an important outcome for patients with erosive oesophagitis and/or complications.[1] It is well established, however, that the majority of patients, regardless of endoscopic status, will experience relapse within 6 months of cessation of short-term acid suppressant therapy.[2, 3] Maintenance therapy with a proton pump inhibitor is therefore widely recommended, with treatment ideally utilizing the minimal drug dose required to

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relieve symptoms and maintain mucosal healing.[4] However, the choice of therapy for long-term management of GERD should also consider patient preference and opinion.[5] If symptoms are infrequent, then 'on-demand' therapy may offer a reasonable approach to management. Indeed, patients prescribed regular long-term medication for GERD often only take it when symptoms recur.[6] On-demand therapy with a proton pump inhibitor may therefore represent a valid option for the long-term management of such patients, particularly as this is probably the method used by many patients.[7]

Esomeprazole, the S-isomer of omeprazole, is the first proton pump inhibitor to be developed as an optical isomer for the treatment of acid-related disorders. This agent displays a similar mechanism of action to omeprazole and is a highly effective inhibitor of gastric acid secretion.[8] Esomeprazole is subject to less extensive first-pass metabolism than omeprazole, resulting in higher systemic bioavailability.[8] This profile translates into a more effective and longer-lasting inhibition of gastric acid secretion over the 24-h dosing interval.[9] Furthermore, esomeprazole is associated with less pronounced interindividual variation in intragastric pH, and might therefore be expected to produce a more consistent clinical response.[9] Together, these properties of esomeprazole have been shown to translate into superior clinical efficacy in oesophagitis compared with omeprazole[10, 11] and may make it particularly suitable for on-demand use in patients with GERD.

The aim of this placebo-controlled study was to determine the efficacy and tolerability of on-demand treatment with esomeprazole 20 mg in maintaining symptom control over a 6-month period, following complete resolution of heartburn, in patients with endoscopy-negative GERD.

METHODS

Patients

Male and female patients with endoscopy-negative GERD were recruited from a previous short-term comparative study of esomeprazole or omeprazole therapy. Only those patients completing the latter study, and who had achieved complete resolution of heartburn (defined by the absence of heartburn during the last 7 days of the 4-week treatment period), were eligible for inclusion (see Figure 1). Patients who required concomitant therapy with nonsteroidal anti-inflammatory drugs, salicylates (> 165 mg daily), diazepam, quinidine, warfarin, diphenylhydantoins, mephenytoin, anticholinergics or prostaglandin ana-

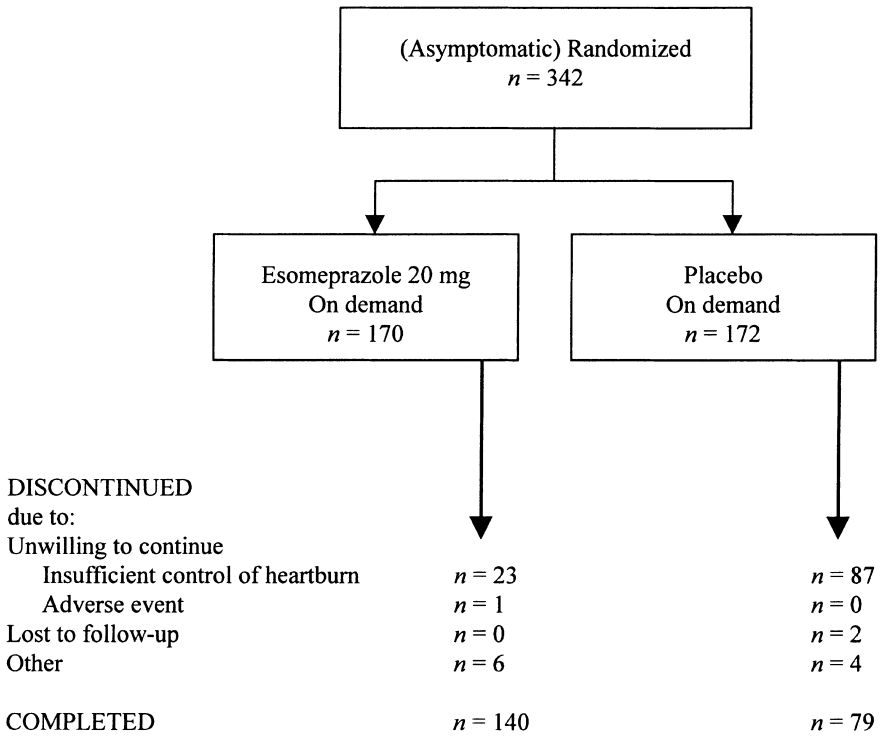

Figure 1. Flow chart for patients in the study.

logues were excluded. Informed written consent was obtained from all patients.

Study design

This was a multicentre, randomized, double-blind, parallel-group study of on-demand treatment with esomeprazole 20 mg or placebo for 6 months or until study discontinuation. Patients were enrolled in the study at 65 centres in Denmark, Finland, Norway and Sweden. The study was performed according to the ethical principles of the Declaration of Helsinki, the protocol having been approved by an independent Ethics Committee for each study centre.

Upon completion of the previous short-term study, eligible patients were randomized (1 : 1) to on-demand oral therapy with identical esomeprazole 20 mg or placebo capsules. Patients were instructed to take one capsule daily, if required, for the relief of heartburn, and to stop treatment when their heartburn was adequately controlled. Patients were provided with antacids (Maalox tablets) as rescue medication. Use of other antacids or *Helicobacter pylori* eradication therapy during the study was prohibited.

Following randomization, patients' symptoms were re-assessed after 2, 4 and 6 months of on-demand therapy. Symptoms were assessed by the investigator according to a standardized checklist, which included the frequency of heartburn (number of days with heartburn during the previous 7 days), heartburn severity (none to severe), and the severity of other GERD symptoms (regurgitation and dysphagia) and other gastrointestinal symptoms (epigastric pain, nausea and vomiting) during the 7 days prior to the visit. A physical examination and assessment of routine laboratory safety variables (blood and urine), initially performed on entry into the previous short-term study (at which time patients' medical histories and baseline demographic data were also recorded), was repeated at the patient's final visit. This corresponded to the completion of 6 months on-demand therapy or study discontinuation, whichever occurred sooner. Laboratory variables were also assessed after 2 months of on-demand treatment. Sampling for assessment of *H. pylori* status with ^{13}C-urea breath testing was carried out in all patients before commencing treatment in the previous study. Adverse events (whether spontaneous, elicited by questioning or observed by the investigator) were recorded at each study visit. Returned study drugs and antacids were counted at each visit. Patients' dosing habits were also assessed by means of the Medical Event Monitoring System (MEMS; APREX Ltd, Zug, Switzerland), which utilizes microelectronic devices recessed in the cap of drug containers. The date and time of each opening and closure of the container is automatically recorded, providing a detailed electronic record of drug intake (i.e. number of container openings).

Statistical analysis

The primary variable in the present study was time to discontinuation of on-demand therapy due to unwillingness to continue, as utilized in an omeprazole study of similar design.[12] The time to study discontinuation due to insufficient control of heartburn was also evaluated (secondary variable).

The power calculation was based on a previous 6-month study with on-demand therapy, in which 56% of placebo recipients completed the full study period.[12] Assuming a corresponding figure of 85% for patients in the esomeprazole 20 mg group, with 100 evaluable patients in each treatment arm, the power of the study was > 99% for a logrank test at the 5% significance level. The study was designed to include all patients with complete resolution of heartburn after 4 weeks' treatment in the previous short-term study, an assumed total of 320 patients (160 patients/group).

For the primary and secondary variables, between-group comparisons were made on an intention-to-treat basis (which included all randomized patients) using life-table methods for graphical presentation and a log-rank test with stratification according to *H. pylori* status. For the purposes of the latter analysis, patients with unknown infection status were classified as *H. pylori*-positive. Other variables, including the severity of specific GERD/other gastrointestinal symptoms, along with patients' dosing habits, were assessed descriptively.

The safety population comprised all patients randomized into the study (regardless of whether or not they took the study drug) for whom post-randomization data were available. Adverse event data were presented descriptively.

RESULTS

A total of 342 patients, asymptomatic after 4 weeks' treatment with esomeprazole 20 mg or omeprazole 20 mg once daily, and ranging in age from 19 to 79 (mean 49) years, were randomized to treatment with

esomeprazole 20 mg ($n = 170$) or placebo ($n = 172$) on demand. The study population comprised slightly more male (56%) than female patients. All patients were Caucasian, and approximately one-third were *H. pylori*-positive. Endoscopy findings proved negative for oesophageal ulcer, stricture and Barrett's metaplasia, although most patients had hiatal hernia. No patient had evidence of peptic ulcer disease, although gastric and/or duodenal erosions were observed in a minor number of patients. Overall, the two treatment groups were well matched with respect to baseline demographic and clinical characteristics (Table 1).

Efficacy of on-demand therapy

A total of 111 patients discontinued the study prematurely due to unwillingness to continue (esomeprazole 20 mg, $n = 24$ [14%]; placebo, $n = 87$ [51%]); this was attributable in all but one case to insufficient control of heartburn (Figure 1). A further 12 patients discontinued participation in the study for other reasons. Therefore, 219 patients completed 6 months of on-demand therapy (esomeprazole 20 mg, $n = 140$ [82%]; placebo, $n = 79$ [46%]).

Comparison of the time to discontinuation due to unwillingness to continue (log-rank test, stratified for *H. pylori* status) showed a statistically significant difference ($P < 0.0001$) in favour of esomeprazole 20 mg over placebo (Figure 2). Similarly, given that insufficient control of heartburn was the reason for unwillingness to continue in virtually all patients who withdrew prematurely in both treatment groups, the analysis of time to discontinuation for this reason (i.e. insufficient control of heartburn) also showed a statistically significant difference ($P < 0.0001$) in favour of esomeprazole 20 mg.

Table 1. Baseline demographics and clinical characteristics of randomized patients (intention-to-treat population)[a]

Characteristic	Treatment group	
	Esomeprazole 20 mg (n = 170)	Placebo (n = 172)
Gender, male : female (%)	55 : 45	57 : 43
Mean age, years (range)	49 (19–78)	49 (21–79)
Mean bodyweight, kg (range)		
Males	83 (56–120)	84 (60–130)
Females	70 (50–100)	73 (54–100)
Frequency of heartburn [no. of patients (%)]		
4 days/week	21 (12)	30 (17)
5 days/week	23 (14)	13 (8)
6 days/week	19 (11)	17 (10)
7 days/week	107 (63)	112 (65)
Heartburn severity [no. of patients (%)]		
Mild	25 (15)	32 (19)
Moderate	117 (69)	112 (65)
Severe	28 (16)	28 (16)
History of heartburn episodes [no. of patients (%)]		
< 6 months	0	1 (1)
6–12 months	11 (6)	17 (10)
1–5 years	55 (32)	44 (26)
> 5 years	104 (61)	110 (64)
Positive *H. pylori* status [no. of patients (%)][b]	64 (38)	57 (33)
Endoscopy findings [no. of patients (%)]		
Oesophageal hiatal hernia	65 (38)	75 (44)
Other oesophageal findings[c]	9 (5)	7 (4)
Gastric erosions	6 (4)	10 (6)

[a] As a result of rounding, percentage values may not always total 100%.
[b] As determined by ^{13}C-urea breath testing.
[c] No patient had oesophageal stricture or Barrett's metaplasia.

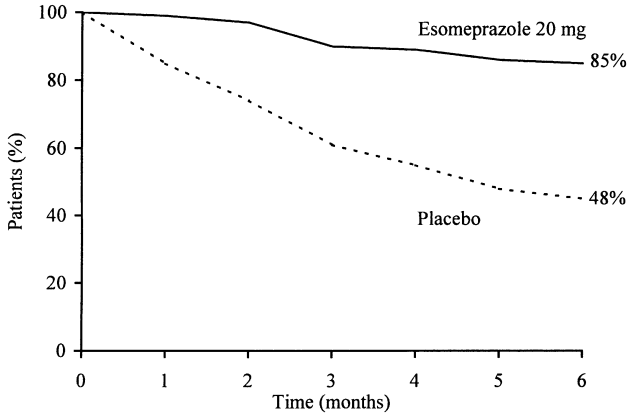

Figure 2. Life-table analysis of time to discontinuation of treatment (due to unwillingness to continue) provided an estimated percentage of the number of patients continuing on therapy during 6 months on-demand treatment with either esomeprazole 20 mg or placebo for endoscopy-negative gastro-oesophageal reflux disease (intention-to-treat population).

The proportion of patients discontinuing treatment due to unwillingness to continue was lower for *H. pylori*-positive patients (21% overall; esomeprazole 5% vs. placebo 40%) compared with *H. pylori*-negative patients (38% overall; esomeprazole 19% vs. placebo 56%). The overall difference and the difference between the two esomeprazole groups was statistically significant ($P = 0.002$ and $P = 0.01$, respectively).

Patients were instructed to take study medication only when experiencing symptomatic relapse, therefore it was of interest to study the number of consecutive days when medication was administered (as shown by MEMS recordings of the number of container openings). Overall, 52% of patients in the esomeprazole 20 mg group took the study medication for at most 3 consecutive days at a time, compared with only 29% of placebo recipients ($P < 0.0001$). However, the proportion of patients who took the study medication for a longer period of time was higher in the placebo group than in the esomeprazole 20 mg group (32% vs. 22%, respectively [$P = 0.04$] took the study medication for 4–6 consecutive days; 21% vs. 11% [$P = 0.03$] took study medication for 7–13 consecutive days). In addition, mean intake of the study medication (i.e. mean number of container openings per day) was significantly higher in the placebo group than in the esomeprazole group (0.41 vs. 0.34, $P = 0.01$). These findings reflect the frequency of heartburn during the study. Thus, a considerably higher proportion of placebo patients (51%) than esomeprazole patients (14%) discontinued treatment due to insufficient heartburn control. Furthermore, 50% of the randomized patients in the esomeprazole group completed the 6-month study with no more than 1 day of heartburn in the previous 7 days compared with 27% in the placebo group ($P < 0.0001$).

In order to calculate mean consumption of rescue antacids, the number of antacid tablets consumed (number of tablets dispensed minus number of tablets returned) was divided by the actual number of days spent in the study. Overall, total antacid usage among evaluable patients (esomeprazole 20 mg, $n = 157$; placebo, $n = 155$) was more than 2-fold higher in the placebo group than in the esomeprazole 20 mg group (mean 1.06 antacid tablets per day with placebo vs. 0.39 with esomeprazole 20 mg, $P = 0.0001$). Not unexpectedly, mean antacid usage was higher among patients discontinuing the study prematurely (1.04 and 1.54 tablets/day for the esomeprazole and placebo groups, respectively) than in those remaining in the study (0.30 and 0.59 tablets/day for the esomeprazole and placebo groups, respectively).

Other variables evaluated in the present study included the severity of heartburn and other GERD symptoms, along with the severity of other gastrointestinal symptoms. The overall findings were consistent with clinical experience, i.e. cessation of continuous acid suppressant therapy resulted in recurrence of GERD symptoms in some patients, as exemplified by the findings for heartburn severity. However, consistently at the three clinical visits after randomization, approximately 65% (64–69%) of the patients in the esomeprazole group had no or only mild heartburn in the previous 7 days, compared with approximately 35% (33–37%) in the placebo group (Table 2).

Safety and tolerability

Of the 342 patients randomized to treatment, post-randomization data were unavailable for one patient in the placebo group. The safety analysis therefore comprised 341 patients (esomeprazole 20 mg, $n = 170$; placebo, $n = 171$). Life-table analysis for the safety population showed that the estimated proportion of patients completing the study was 83% and 46%, respectively, for the esomeprazole 20 mg and placebo treatment groups. Thus, the mean number of days spent in the study was 39% higher in the esomeprazole 20 mg group (165 days) than in the placebo group (119 days).

Table 2. Severity of heartburn during 6 months on-demand therapy

	Percentage of patients					
	Esomeprazole 20 mg (n = 170)			Placebo (n = 172)		
	2 months	4 months	6 months	2 months	4 months	6 months
None	30	35	34	15	17	21
Mild	35	29	35	22	16	13
Moderate	23	18	10	18	10	11
Severe	2	2	3	5	3	1
Discontinued[a]	10	17	18	40	53	54

[a] Patients discontinued due to severity of heartburn. All other patients remained in the study for its 6-month duration.

On-demand therapy with esomeprazole 20 mg was well tolerated overall. Adverse events were reported by 73 patients (43%) in the esomeprazole 20 mg group and 47 patients (27%) in the placebo group. However, taking into account the shorter exposure time for placebo recipients, the incidence and profile of adverse events was essentially comparable for the two treatment groups. The most commonly reported adverse event in both treatment groups was respiratory infection (esomeprazole 20 mg, $n = 11$ [6%]; placebo, $n = 13$ [8%]); all other specific adverse events were reported in < 5% of patients.

A total of seven patients reported nine serious adverse events during the study: five patients from the esomeprazole 20 mg group reported seven serious adverse events (fever, diarrhoea, vomiting, facial paresis, epigastric pain, hypertensive heart disease with congestive heart failure, pneumonia), while two patients in the placebo group reported two serious adverse events (aggravated Parkinson's disease, abdominal pain). Causality between these events and the study drug was considered unlikely in all cases, and they did not necessitate treatment withdrawal. Two patients discontinued the study as a result of nonserious adverse events (one patient in the esomeprazole 20 mg group experienced moderate chest pain, while another patient on placebo withdrew because of mild nausea; both recovered without sequelae). There were no clinically relevant changes in laboratory safety variables or vital signs during the study.

DISCUSSION

The management of patients with GERD represents a major healthcare problem in the adult population, both clinically and economically. Well over 50% of these patients are endoscopy-negative (i.e. there is no evidence of macroscopic damage to the oesophageal mucosa),[13, 14] and relatively little is known regarding their clinical course following symptom relief with short-term proton pump inhibitor therapy.[12] However, we already understand that many patients, who are subsequently prescribed regular long-term therapy for their condition, typically resort to using such therapy on demand when symptoms recur.[6] Overall, the findings of the current study indicate that on-demand treatment with esomeprazole 20 mg is an effective strategy for maintaining symptom control in patients with endoscopy-negative GERD. Of interest, more patients were unwilling to continue in the *H. pylori* negative subgroup. This is consistent with recent reports that *H. pylori* infection predisposes towards milder forms of GERD.[15, 16] Alternatively, proton pump inhibitors may be more efficacious in those with *H. pylori* and corpus gastritis because of increased intragastric pH.[17]

We used the patient's willingness to continue in the study as an indirect measure of the control of GERD symptoms.[12] At a dosage of 20 mg once daily when required, esomeprazole showed a statistically significant advantage over placebo. Not unexpectedly, similar findings were observed for time to discontinuation due to insufficient control of heartburn (the principal symptom of GERD, as this was the reason for premature discontinuation in virtually all instances). Moreover, esomeprazole was associated with reduced antacid usage compared with placebo, and few patients required treatment for periods of more than 3 consecutive days.

The use of a placebo treatment arm in the current study permits an evaluation of the natural course of endoscopy-negative GERD, because patients are only permitted to take antacids following effective symptom relief with short-term proton pump inhibitor therapy. Overall, 48% of patients demonstrated a willingness to

persist with placebo treatment (in conjunction with antacids) for symptomatic control of heartburn. Thus, over a 6-month period, over half of all patients with endoscopy-negative GERD experience an unacceptable degree of symptomatic relapse that is inadequately controlled by antacids alone. In contrast, 85% of patients were willing to continue with on-demand esomeprazole therapy (20 mg) in the present study. This compares with continuation rates of 69–83% for on-demand omeprazole (10 mg and 20 mg) therapy in a comparable cohort of patients.[12] In that study, 56% of placebo recipients were willing to persist with placebo treatment (in conjunction with antacids) for control of their symptoms, which is not dissimilar to the rate observed in the present study (48%). What the results of these studies suggest is that many patients with endoscopy-negative GERD may not require continuous maintenance therapy for control of their symptoms. This is in contrast to patients with oesophagitis, for whom the outcome of long-term antisecretory therapy is significantly affected by the severity of oesophagitis.[18] For these patients, and in cases of GERD-related complications, continuous maintenance therapy is more likely to be needed.[7]

The emerging differences in optimal management for patients with and without oesophagitis can probably be explained by the extent of underlying acid reflux. Thus, in the absence of oesophagitis, GERD is accompanied by less acid reflux than in patients with reflux oesophagitis.[19] Consequently, on-demand rather than continuous therapy may be a viable long-term management option in this setting, and would have important economic implications, because reduced drug use would translate into reduced treatment costs. One possible limitation of on-demand therapy is that it allows symptoms to recur, although the majority of patients appeared to accept this in the knowledge that effective therapy for symptom control was readily available if required. On-demand therapy therefore provides a more individualized approach to management of the patient with GERD, whereby the patient dictates the extent of drug usage according to his or her specific needs. The increased sense of control conferred by on-demand therapy may partly explain why the great majority of patients were willing to persist with esomeprazole treatment in the present study.

In conclusion, the findings of this study indicate that on-demand therapy with esomeprazole 20 mg is well tolerated and provides effective long-term control of symptoms in patients with endoscopy-negative GERD. Traditionally, such patients would have received maintenance antisecretory therapy, a major cost driver in today's healthcare budgets. A therapeutic approach that utilizes on-demand proton pump inhibitor therapy may therefore lead to significant cost savings. Further studies are required to establish the likely economic advantages of this approach over conventional daily maintenance therapy.

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