

Review article: initial therapy of reflux disease with esomeprazole

J. DENT

Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital, Adelaide, Australia

SUMMARY

Large clinical trials in patients with reflux oesophagitis have shown esomeprazole, 40 mg once daily, to be convincingly superior in the healing of oesophagitis when compared with both omeprazole, 20 mg once daily, and lansoprazole, 30 mg once daily. The greatest advantage for esomeprazole is with healing of the more

severe grades of oesophagitis. Esomeprazole, 40 mg once daily, has also been shown to be significantly superior in the treatment of heartburn. Studies in endoscopy-negative patients, or in both oesophagitis and endoscopy-negative patients, have demonstrated good efficacy for esomeprazole, with high levels of symptom control achieved in the first 7 days of therapy.

INTRODUCTION

A very-large-scale clinical trial programme has gathered a great deal of data on the outcomes of initial treatment of reflux disease with esomeprazole. The first studies compared esomeprazole with omeprazole, but, recently, data have become available that compare esomeprazole with lansoprazole. This article gives an overview of these studies, which show that the superior control of gastric pH with esomeprazole, 40 mg once daily, translates into a useful increment of clinical efficacy when compared with other proton pump inhibitors.

DOUBLE-BLIND, RANDOMIZED STUDIES IN PATIENTS WITH REFLUX OESOPHAGITIS

Comparisons of esomeprazole with omeprazole

Three studies with esomeprazole, 40 mg, performed in the USA, have used essentially the same protocols, so that data from the 4877 patients enrolled can be pooled. The two largest studies by Kahrilas *et al.*¹ ($n = 1247$) and Richter *et al.*² ($n = 2425$) have been

published in full. Oesophagitis healing was evaluated after 4 and, if necessary, 8 weeks of treatment. Symptom responses were evaluated during the first 4 weeks of treatment. *Helicobacter pylori* infection was screened for with serology; if positive, patients were excluded from the studies. As expected, other tests for *H. pylori* infection subsequent to enrolment showed that 8.9% of patients who were serology-negative were infected with *H. pylori*. These patients remained in the studies.

The major emphasis of these studies was to compare esomeprazole, 40 mg once daily, with omeprazole, 20 mg once daily. The esomeprazole dose was chosen on the basis of its superior effects on gastric pH when compared with omeprazole and esomeprazole, 20 mg once daily (see elsewhere in these supplement).

The total pooled data for healing of oesophagitis with esomeprazole, 40 mg once daily, compared with omeprazole, 20 mg once daily, are shown in Figure 1 for 4 and 8 weeks.^{1, 2} There was convincing superiority ($P < 0.001$) in favour of esomeprazole over omeprazole. This superiority was most evident in patients with severe oesophagitis before treatment, defined as either Los Angeles Grades C or D,³ as shown in Figure 2. The verbal description of these grades of oesophagitis is as follows:

- Grade C: 'one (or more) mucosal break that is continuous between the tops of two or more mucosal

Correspondence to: Professor J. Dent, Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital, Adelaide, SA 5000, Australia.
E-mail: jdent@mail.rah.sa.gov.au

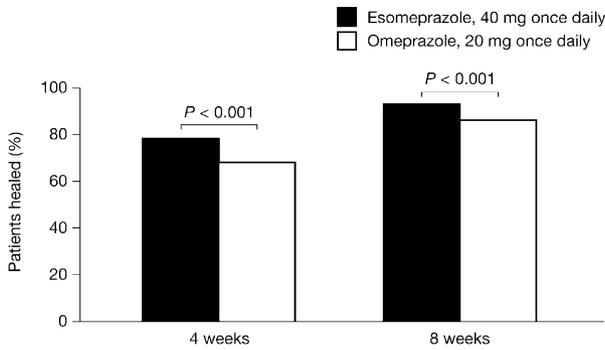


Figure 1. Pooled data comparing the healing rates of esophagitis with esomeprazole, 40 mg once daily, and omeprazole, 20 mg once daily. Data are from the total published^{1, 2} ($n = 3672$) and as yet unpublished ($n = 1205$) database held on file at AstraZeneca.

...folds, but which involves less than 75% of the circumference’;

- **Grade D:** ‘one (or more) mucosal break, which involves at least 75% of the oesophageal circumference’.

Data on oesophagitis healing rates according to pre-treatment oesophagitis grade from Kahrilas *et al.*¹ resembled those of Richter *et al.*² shown in Figure 2.

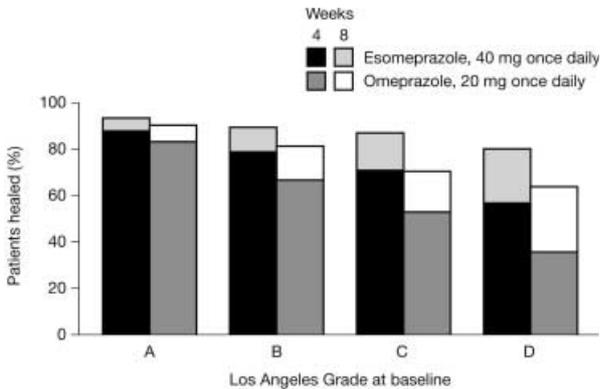


Figure 2. Cumulative healing rates of oesophagitis after 4 and 8 weeks of treatment with esomeprazole, 40 mg once daily, or omeprazole, 20 mg once daily ($n = 2425$). Healing rates with esomeprazole at 4 weeks are very similar to those with omeprazole at 8 weeks. Healing rates in patients with Los Angeles Grades C and D are markedly superior with esomeprazole. From Richter *et al.*² Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol* 2001; 96: 656–65, Copyright © 2001 by American Gastroenterological Association, reproduced with permission from W.B. Saunders, an imprint of Elsevier Science (USA).

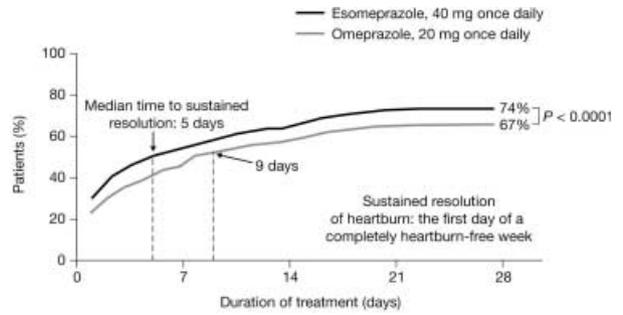


Figure 3. Time taken to reach sustained resolution of heartburn ($n = 1247$); see the figure for the definition of this outcome measure. From Kahrilas *et al.*¹ with permission.

Esomeprazole, 40 mg once daily, also produced a superior response in the resolution of heartburn, when compared with omeprazole, 20 mg once daily. Data for sustained resolution of heartburn from the study by Kahrilas *et al.*¹ and the definition of this outcome measure, are shown in Figure 3. The median time to sustained resolution was almost halved. Similar data have been reported by Richter *et al.*² The superiority of esomeprazole, 40 mg once daily, was also demonstrated by a higher proportion of patients free of heartburn at 4 weeks, when compared with omeprazole, 20 mg once daily (65% vs. 57%, $P < 0.005$;¹ 68% vs. 58%, $P < 0.001$ ²).

Comparison of esomeprazole with lansoprazole

A recently published study by Castell *et al.* in 5241 patients compared the outcomes of initial therapy of reflux oesophagitis with esomeprazole, 40 mg once daily, and lansoprazole, 30 mg once daily, at 4 and 8 weeks.⁴ This US study had a protocol that was almost identical to the esomeprazole/omeprazole comparisons, except that there was no requirement to screen for and exclude *H. pylori*-infected patients.

The cumulative healing rate at 8 weeks, the primary outcome measure, was superior for esomeprazole-treated patients compared with lansoprazole-treated patients (92.6% vs. 88.8%, $P = 0.0001$). Healing rates at 8 weeks according to pre-treatment oesophagitis grade are shown in Figure 4. As with the omeprazole comparisons, the greater efficacy of esomeprazole is most evident in patients with severe oesophagitis. The 4-week healing rate of 79.4% with esomeprazole was also significantly higher than the 75.1% healing rate with lansoprazole ($P = 0.0001$).

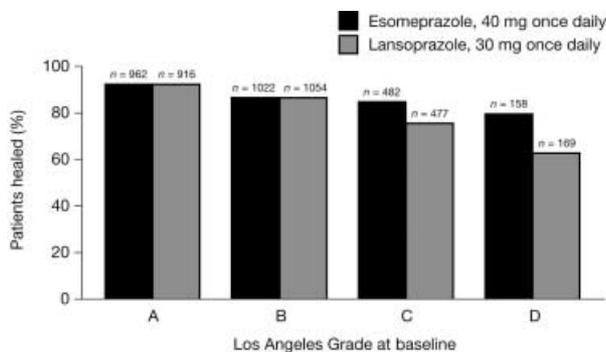


Figure 4. Cumulative healing rates at 8 weeks with esomeprazole, 40 mg once daily, and lansoprazole, 30 mg once daily, according to endoscopic grade ($n = 5241$; one patient in the lansoprazole group did not have oesophagitis according to the LA classification). These data show the convincing superiority of esomeprazole in patients with Los Angeles Grades C and D oesophagitis. Adapted from Castell *et al.*⁴ Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. *Am J Gastroenterol* 2002; 97: 575–83. Copyright © 2002 by American Gastroenterological Association, reproduced with permission from W.B. Saunders, an imprint of Elsevier Science (USA).

DOUBLE-BLIND, RANDOMIZED STUDIES IN PATIENTS WITH ENDOSCOPY-NEGATIVE REFLUX DISEASE

Esomeprazole, 20 mg or 40 mg once daily, for 4 weeks has been compared with placebo in two US studies in 717 endoscopy-negative reflux disease patients.⁵ Esomeprazole, 40 mg once daily, was no better than esomeprazole, 20 mg once daily, with both giving a good response of resolution of heartburn, which was significantly ($P < 0.001$) superior to placebo.

Esomeprazole, 40 mg, and placebo have also been compared in a mixed group of oesophagitis and endoscopy-negative patients over a 2-week assessment period.⁶ The primary aim of this Scandinavian study was to determine the value of esomeprazole, 40 mg once daily in the morning, or esomeprazole, 20 mg twice daily, as a confirmatory test of therapy. The two esomeprazole dosing regimens gave identical and convincing resolution of heartburn, which reached a plateau after 7–8 days of therapy.

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