

## Review article: esomeprazole in the treatment of *Helicobacter pylori*

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### SUMMARY

Proton pump inhibitor-based triple therapy is the most commonly used treatment for eradication of *Helicobacter pylori*, with pooled eradication rates of approximately 90%. In the USA, per protocol eradication rates with 10-day proton pump inhibitor-based triple therapy are approximately 85%. Esomeprazole, a new proton pump inhibitor that is the S-isomer of omeprazole and produces a greater inhibition of acid secretion than omeprazole, has recently been evaluated in the treatment of *H. pylori*. Seven-day twice daily triple therapy with esomeprazole 20 mg,

amoxicillin 1 g and clarithromycin 500 mg provided intention-to-treat eradication rates of 86–90% and per protocol eradication rates of 90–91% in duodenal ulcer patients in Europe and Canada. Ten-day triple therapy with esomeprazole 40 mg q.d.s., amoxicillin 1 g b.d. and clarithromycin 500 mg b.d. achieved intention-to-treat eradication rates of 77–78% and per protocol eradication rates of 84–85% in USA duodenal ulcer patients. Thus, esomeprazole triple therapy with amoxicillin and clarithromycin is effective in the treatment of *H. pylori*, with eradication rates comparable to previously studied proton pump inhibitor-based triple therapies.

### INTRODUCTION

Triple therapy with a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole is the most commonly used *H. pylori* eradication regimen among gastroenterologists.<sup>1</sup> Systematic reviews indicate that 1 week of twice daily proton pump inhibitor, clarithromycin and amoxicillin or metronidazole achieves per protocol eradication rates of approximately 90%.<sup>2</sup> In the USA, prospective, double-blind trials have demonstrated that 10-day twice-daily triple therapy with omeprazole or lansoprazole, clarithromycin and amoxicillin achieves per protocol eradication rates of 84–85%.<sup>3–5</sup>

Proton pump inhibitors have two potential mechanisms of action in the treatment of *H. pylori*. They have antibacterial activity, and, by reducing gastric acid secretion, they increase the availability and activity of some antibiotics. Increasing proton pump inhibitor dose

or frequency has been documented to increase eradication rates in dual therapy with amoxicillin<sup>6, 7</sup> and in proton pump inhibitor-based triple therapy.<sup>2, 8, 9</sup>

Omeprazole, which prevents acid production by blocking the parietal cell H<sup>+</sup>/K<sup>+</sup>-ATPase (the 'proton pump'), is administered as a racemic mixture of its two optical isomers, S-omeprazole and R-omeprazole.<sup>10</sup> The S-isomer of omeprazole, esomeprazole, produces greater gastric acid inhibition than omeprazole due to its increased bioavailability.<sup>10</sup> In addition, less interpatient variability in acid inhibition is seen with esomeprazole.<sup>10</sup> This article will review randomized controlled trials which have evaluated the efficacy of esomeprazole in the treatment of *H. pylori*.

Five double-blind, randomized, prospective, controlled trials have been conducted with esomeprazole-based therapy. Seven-day esomeprazole-based triple therapy was assessed in patients with active duodenal ulcer disease in Eastern Europe<sup>11</sup> and in patients with prior duodenal ulcer disease in Europe and Canada.<sup>12</sup> Ten-day esomeprazole monotherapy, dual therapy and triple therapy were assessed in patients with active or prior duodenal ulcer disease in three US studies.<sup>13</sup>

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### SEVEN-DAY TRIPLE THERAPY FOR ACTIVE DUODENAL ULCER<sup>11</sup>

Patients with active duodenal ulcer at endoscopy and *H. pylori* documented by two of three *H. pylori* tests (rapid urease test, biopsy or urea breath test) were randomly assigned to a 7-day course of amoxicillin 1000 mg, clarithromycin 500 mg, and either esomeprazole 20 mg or omeprazole 20 mg. After 1 week of therapy, patients in the omeprazole arm received omeprazole 20 mg daily for 4 weeks, while patients in the esomeprazole group received placebo for 4 weeks. Endoscopy was repeated at the end of this 4-week period and again 4 weeks later. *H. pylori* eradication rates (assessed at the last visit) were comparable for omeprazole vs. esomeprazole (intention-to-treat: 88% vs. 86%; per protocol: 90% vs. 89%) (Table 1). Ulcer healing (assessed at the 4-week endoscopy) was also comparable for omeprazole vs. esomeprazole (intention-to-treat: 92% vs. 91%; per protocol: 96% vs. 94%). Withdrawals due to side-effects were seen in 3/224 (1.3%) patients treated with omeprazole triple therapy and 1/222 (0.5%) of the esomeprazole triple therapy group.

### SEVEN-DAY TRIPLE THERAPY FOR PRIOR DUODENAL ULCER<sup>12</sup>

Patients with a past duodenal ulcer documented by endoscopy or radiography and *H. pylori* infection documented by positive rapid urease test and urea breath test were randomly assigned to omeprazole or esomeprazole triple therapy as in the active duodenal ulcer study. Repeat urea breath tests were done at 4 and 8 weeks after the completion of the triple therapy. Patients were considered *H. pylori* negative only if both breath tests were negative. *H. pylori* eradication rates were comparable for omeprazole vs. esomeprazole (intention-to-treat: 88% vs. 90%; per protocol: 91%

Table 1. *H. pylori* intention-to-treat and per protocol eradication rates with 95% confidence intervals following 7-day triple therapy for active duodenal ulcer<sup>11</sup>

	EAC	OAC
Intention-to-treat	184/195 (86%, 81–90%)	192/202 (88%, 83–92%)
Per protocol	176/190 (89%, 84–93%)	180/194 (90%, 85–93%)

E = esomeprazole 20 mg b.d., O = omeprazole 20 mg b.d., A = amoxicillin 1 g b.d., C = clarithromycin 500 mg b.d.

Table 2. *H. pylori* intention-to-treat and per protocol eradication rates with 95% confidence intervals with 7-day triple therapy for prior duodenal ulcer<sup>12</sup>

	EAC	OAC
Intention-to-treat	183/204 (90%, 85–94%)	172/196 (88%, 82–92%)
Per protocol	174/192 (91%, 86–94%)	169/185 (91%, 86–95%)

E = esomeprazole 20 mg b.d., O = omeprazole 20 mg b.d., A = amoxicillin 1 g b.d., C = clarithromycin 500 mg b.d.

vs. 91%) (Table 2). Withdrawal due to side-effects were identical in the two study groups: 4/224 (1.8%).

### TEN-DAY THERAPIES FOR ACTIVE OR PRIOR DUODENAL ULCER IN USA<sup>13</sup>

Patients with active duodenal ulcer at endoscopy (representing 80% of the study group) or a prior history of duodenal ulcer documented by endoscopy or radiography were eligible if rapid urease test plus histologic exam or culture was positive. In all three US studies esomeprazole was given at a daily dose of 40 mg, while amoxicillin was given at 1 g b.d. and clarithromycin at 500 mg b.d. In all studies, endoscopy with rapid urease testing, histology and culture was repeated 4 weeks after the completion of the 10-day course of treatment. In the first study, esomeprazole, amoxicillin and clarithromycin triple therapy was compared to esomeprazole plus clarithromycin dual therapy. Esomeprazole triple therapy was compared to esomeprazole monotherapy in the second study, and esomeprazole dual therapy was compared to esomeprazole monotherapy in the third study. Results (Table 3) showed eradication rates with esomeprazole triple therapy of 77–78% by intention-to-treat analysis and 84–85% for per protocol analysis. Dual therapy eradication rates were 46–52% by intention-to-treat analysis and 50–55% by per protocol analysis (Table 3). Withdrawals due to side-effects were seen in 10/307 (3.6%) taking esomeprazole triple therapy, 11/265 (4.2%) taking dual therapy, and 1/40 (2.5%) taking esomeprazole alone.

Antibiotic susceptibility testing was performed in the US studies. Fifteen per cent of the patients were *H. pylori* infection, which was resistant to clarithromycin at baseline. The eradication rate with esomeprazole triple therapy in patients with susceptible strains was 89% as compared to 45% in those with resistant strains. Eradication rates for dual therapy were 61% and 13%,

Table 3. *H. pylori* intention-to-treat and per protocol eradication rates and 95% confidence intervals in US studies of 10-day esomeprazole-based therapy for active or prior duodenal ulcer<sup>1,3</sup>

	Study 1		Study 2		Study 3	
	EAC	EC	EAC	E	EC	E
Intention-to-treat	179/233 <sup>a</sup> (77%, 71–82%)	112/215 (52%, 45–59%)	58/74 <sup>b</sup> (78%, 68–87%)	1/24 (4%, 0–21%)	23/50 <sup>c</sup> (46%, 32–61%)	0/16 (0%, 0–21%)
Per protocol	164/196 <sup>a</sup> (84%, 78–89%)	103/187 (55%, 48–62%)	57/67 <sup>b</sup> (85%, 74–93%)	1/22 (5%, 0–23%)	22/44 <sup>c</sup> (50%, 35–65%)	0/15 (0%, 0–22%)

E = esomeprazole 40 mg q.d.s., A = amoxicillin 1 g b.d., C = clarithromycin 500 mg b.d.

<sup>a</sup>*P* < 0.001, EAC vs. EC; <sup>b</sup>*P* < 0.001, EAC vs. E; <sup>c</sup>*P* < 0.05, EC vs. E.

respectively. An emergence of clarithromycin resistance after unsuccessful treatment in patients with baseline clarithromycin susceptibility was seen in 23/27 (85%) of patients in the dual therapy group and in 2/6 (33%) of the triple therapy group.

## DISCUSSION

The double-blind randomized trials performed with esomeprazole documented that esomeprazole triple therapy with amoxicillin and clarithromycin was effective in the treatment of *H. pylori*. Studies which have primarily included European patients reveal that 7-day triple therapy with esomeprazole 20 mg twice daily achieves eradication rates of approximately 90%, which is comparable to those with other proton pump inhibitor-based triple therapies.<sup>2</sup> In the USA, the eradication rate of 84–85% with a 10-day triple therapy using esomeprazole 40 mg once daily is identical to rates seen with 10-day triple therapies using omeprazole 20 mg or lansoprazole 30 mg twice daily.<sup>3–5</sup>

The study from Tulassay *et al.*<sup>11</sup> also assessed whether proton pump inhibitor therapy needed to be continued after a course of *H. pylori* therapy in patients with active duodenal ulcer. In this double-blind trial, ulcer healing was comparable whether patients received an additional 3 weeks of proton pump inhibitor or placebo after 7 days of triple therapy. Ulcer healing at 4 weeks was comparably good (> 90%) in both study groups, suggesting that patients with duodenal ulcers do not require additional proton pump inhibitor therapy after *H. pylori* eradication therapy. However, a previous study from Labenz *et al.*<sup>14</sup> raised the possibility that healing may be more rapid in patients receiving additional proton pump inhibitor therapy. In this smaller double-blind trial, patients received 3 weeks of placebo or omeprazole after 1 week of proton pump inhibitor triple

therapy. Ulcer healing at 2 weeks was lower in the group receiving placebo (91% vs. 76%, *P* = 0.14), while ulcer healing at 4 weeks was 100% in both groups. Relief from dyspepsia was similar in the placebo and proton pump inhibitor groups at 2 and 4 weeks. Thus, the results from Tulassay *et al.* and earlier studies suggest that patients with active duodenal ulcer disease who receive effective *H. pylori* therapy may not benefit from additional antisecretory therapy.

In summary, esomeprazole-based *H. pylori* triple therapy with amoxicillin and clarithromycin provides an efficacy which is comparable to previously studied proton pump inhibitor-based triple therapies. Whether increasing the dose or frequency of esomeprazole would further increase eradication rates deserves further study.

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