Aliment Pharmacol Ther 2005; 21: 795–804. doi: 10.1111/j.1365-2036.2005.02418.x

Systematic review and meta-analysis: is 1-week proton pump inhibitor-based triple therapy sufficient to heal peptic ulcer?

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Accepted for publication 28 January 2005

SUMMARY

Aims: To systematically review the efficacy on ulcer healing of 1-week combination of a proton pump inhibitor plus two antibiotics and to perform a meta-analysis of randomized clinical trials to evaluate whether 7 days of proton pump inhibitor-based triple therapy is sufficient to heal peptic ulcer.
Methods: Studies where 1-week proton pump inhibitor-based triple therapy was administered to heal peptic ulcer were included. Randomized clinical trials comparing the efficacy on ulcer healing of 7-day proton pump inhibitor-based triple therapy versus this same regimen but prolonging the proton pump inhibitor for several more weeks were included in the meta-analysis. Electronic and manual bibliographical searches were conducted. Meta-analysis was performed combining the odds ratios of the individual studies.
Results: Twenty-four studies (2342 patients) assessed ulcer healing with 1-week proton pump inhibitor-based triple therapy. Mean healing rate was 86%, and 95% in *Helicobacter pylori*-eradicated patients. Six studies (862 patients), were included in the meta-analysis. Mean ulcer healing rate with a 7-day treatment was 91% versus 92% when proton pump inhibitor was prolonged for 2–4 more weeks (odds ratio = 1.11; 95% confidence interval = 0.71–1.74).
Conclusion: In patients with peptic ulcer and *H. pylori* infection, prolonging therapy with proton pump inhibitor after a triple therapy for 7 days with a proton pump inhibitor and two antibiotics is not necessary to induce ulcer healing.

INTRODUCTION

Before the discovery of *Helicobacter pylori*, gastroduodenal ulcer healing was achieved with the administration of H_2-blockers or proton pump inhibitors (PPIs) for at least 4 weeks. At present, it is clear that *H. pylori* eradication therapy is totally indicated in gastroduodenal ulcer disease.[1] This recommendation is based mainly on the reduction of ulcer recurrence after eradication of the organism.[2–4] Another advantage of eradication therapy is that it facilitates ulcer healing,[2–4] eradication of *H. pylori* being a surrogate marker for peptic ulcer cure.[5] Moreover, eradicating the organism has been reported to heal ulcers refractory to conventional antisecretory therapy.[6–8]

General agreement exists in that eradication of *H. pylori* infection with triple therapy including a PPI and two antibiotics for 7–10 days is the gold standard of treatment.[1] Nevertheless, while eradication of *H. pylori* is an appropriate end-point for clinical trials in patients with peptic ulcer disease,[9] ulcer healing and relief of symptoms are the primary aims of treatment from the patient's perspective. The traditional strategy in peptic ulcer disease has been therefore to continue PPI monotherapy for a further 3 weeks after *H. pylori* eradication to ensure ulcer healing and symptom relief.

However, the optimal treatment of *H. pylori* is still a matter of debate. As mentioned, most ulcer patients have

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been traditionally treated with antisecretory drugs up to follow-up investigation 4 or more weeks after cessation of anti-*H. pylori* therapy, and it has been controversial whether eradication of *H. pylori* alone, without acid suppression, is sufficient to achieve the goal of both good efficacies in *H. pylori* eradication and peptic ulcer healing. This represents an important issue because there is a significant correlation between the complexity and duration of treatment, on one hand, and the cost of treatment and patient compliance, on the other.

Our aims were to: (i) systematically review the efficacy on ulcer healing of one-week combination of a PPI plus two antibiotics and (ii) to perform a meta-analysis of randomized clinical trials comparing the efficacy on ulcer healing of this eradication regimen with and without prolonging the PPI after 1 week, to evaluate whether 7 days of PPI-based triple therapy is sufficient to heal peptic ulcer.

METHODS

Selection of studies

Clinical trials where *H. pylori* eradication treatment with 1-week PPI-based triple therapy was administered not only to cure *H. pylori* infection but also to heal peptic ulcer disease (duodenal or gastric ulcer) were included in this systematic review. The presence of the ulcer had to be documented endoscopically. Studies with all patients taking non-steroidal anti-inflammatory drugs were excluded. Only studies that clearly stated information about the number of treated patients and the number of patients with ulcer healing success were selected. For the meta-analysis, randomized clinical trials comparing the efficacy on ulcer healing of 7-day combination of a PPI plus two antibiotics vs. this same regimen but prolonging the PPI for several more weeks were included. The outcome considered in this review was 'ulcer healing success'.

Search strategy for identification of studies

Trials were identified by searching the Cochrane Library (Issue 3 – 2004), MEDLINE (August 2004), EMBASE (August 2004) and CINAHL (August 2004). A search strategy was constructed by using a combination of the following words: (*Helicobacter pylori* OR *H. pylori*) AND (heal OR heals OR healed OR healing OR 'ulcer healing' OR 'ulcer-healing'). Articles published in any language except Japanese were included. Reference lists from the trials selected by electronic searching were hand-searched to identify further relevant trials. Reviewing articles examining the role of *H. pylori* infection on gastroduodenal ulcer healing were also searched to identify articles which met the inclusion criteria.

Assessment of study quality

The quality of the studies included in the meta-analysis was assessed using the score proposed by Jadad *et al.*[10] based on three items: (1) randomization; (2) double blinding and (3) description of withdrawals and dropouts. The items were presented as questions to elicit yes or no answers. Points awarded for items 1 and 2 depended on the quality of the description of the methods to generate the sequence of randomization and/or on the quality of the description of the method of double blinding. If the trial had been described as randomized and/or double blind, but there was no description of the methods used to generate the sequence of randomization or the double blinding conditions, one point was awarded in each case. If the method of generating the sequence of randomization and/or blinding had been described, one additional point was given to each item if the method was appropriate. A method to generate randomization sequences was regarded as adequate if it allowed each study participant to have the same chance of receiving each intervention, and if the investigators could not predict which intervention was next. Double blinding was considered appropriate if it was stated or implied that neither the person doing the assessment nor the study participant could identify the intervention being assessed. Conversely, if the method of generating the sequence of randomization and/or blinding was described but not appropriate, the relevant item was given zero points. The third item, withdrawals and dropouts, was awarded as zero points for a negative answer and one point for a positive. For a positive answer, the number of withdrawals and dropouts and the reasons had to be stated in each of the comparison groups. If there were no withdrawals, it should have been stated in the report.

Data extraction

The following variables were extracted in a predefined data extraction form (see Table 1): author, number of

Table 1. Studies assessing ulcer healing with 7-day combination of a proton pump inhibitor (PPI) plus two antibiotics

Author	Number of patients	Ulcer type	Treatment	Overall ulcer healing (%)	Ulcer healing in eradication success (%)
Adamek *et al.*[11]	9	DU, GU	PPI + C + M	100	100
Colin *et al.*[12]	67	DU	PPI + C + A	87	90
Forne *et al.*[13]	91	DU	PPI + C + A	91	95
Garcia *et al.*[14]	122	DU, GU	PPI + C + A	90	98
Gisbert *et al.*[15]	182	DU	PPI + C + A, PPI + C + M, PPI + A + M	81	90
Goh *et al.*[16]	37	DU, GU	PPI + C + A	84‡	93‡
Goh *et al.*[17]	47	DU, GU	PPI + C + A	89‡	95‡
Gomollon *et al.*[18]	92	DU	PPI + C + A	92	97
Jaup *et al.*[19]	41	DU, GU	PPI + C + M	100	100
Jaup *et al.*[20]	22	DU, GU	PPI + C + M, PPI + C + T	100	100
Harris *et al.*[21]	262	DU	PPI + C + A, PPI + C + M, PPI + A + M	82	94
Higuchi *et al.*[22]	61	GU	PPI + C + A	49	
Hsu *et al.*[23]	39	DU, GU	PPI + C + M	89	94
Labenz *et al.*[24]	112	DU, GU	PPI + C + A, PPI + C + M, PPI + A + M, PPI + C + T	95	97
Labenz *et al.*[25]	29	DU	PPI + C + M	100	100
Marzio *et al.*[26]	53	DU	PPI + C + M	83	95
Schütze *et al.*[27]	45	DU	PPI + C + A	91	98
Schütze *et al.*[28]	77	DU	PPI + C + M	90	98
Spinzi *et al.*[29]	356	DU, GU	PPI + C + A	86	
Spinzi *et al.*[30]	95	DU	PPI + C + A	85	
Sung *et al.*[31]	50	DU	PPI + C + A	90	
Tepes *et al.*[32]	35	DU	PPI + C + A	88	
Tulassay *et al.*[33]	222	DU	PPI + C + A	91	
Wheeldon *et al.*[34]	99	DU, GU	PPI + C + M*	79	
Wheeldon *et al.*[34]	97	DU, GU	PPI + C + M†	68	

Ulcer healing was considered by intention-to-treat analysis, except when otherwise indicated (‡ per-protocol analysis).
DU, duodenal ulcer; GU, gastric ulcer; C, clarithromycin; M, metronidazole; A, amoxicillin; T, tetracycline.
* Twice-daily regimen.
† Once-daily regimen.
Healing rate (weighted mean) was 86% (95% confidence interval, 84–87%) considering all patients, and 95% (95% confidence interval, 94–96%) when only patients with *Helicobacter pylori* eradication success were considered.

patients included, ulcer type (duodenal or gastric), type of *H. pylori* eradication regimen (PPI plus antibiotics), and ulcer healing rate (both overall ulcer healing and in patients with *H. pylori* eradication success). Additionally, in studies included in the meta-analysis, the following variables were also extracted: methods of the study (randomization and double blinding), type and dose of PPI, type and dose of antibiotics, additional PPI dose and time (after eradication regimen), time at ulcer healing assessment, and quality score (see Jadad score in previous section, including items of randomization, double blinding, and description of withdrawal/dropouts).

Data synthesis

The outcome considered in this study was 'ulcer healing rate'. The mean percentage of patients with ulcer healing was calculated and expressed as weighted mean

[and corresponding 95% confidence interval (95% CI)] to make due allowance for the number of patients included in each study. For the meta-analysis, the homogeneity of effects throughout studies was appraised using a homogeneity test based on the chi-square test. Because of the low power of this test, a minimum cut-off *P*-value of 0.1 was established as a threshold of homogeneity: lower values indicated heterogeneity, and prevented us from relying on the combination of the study results. Meta-analysis was performed combining the odds ratios (OR) of the individual studies in a global OR, using a random effect model (DerSimonian and Laird). Significance and 95% CI are provided for the combined OR. All calculations were performed with the freeware program Review Manager 4.2.3.

Subanalysis/sensitivity analysis

Subanalyses were planned *a priori* depending on the ulcer type (duodenal or gastric) and the quality of the studies (based on quality score proposed by Jadad, see appropriate section).

RESULTS

Description of studies and efficacy on ulcer healing

Studies assessing ulcer healing with a 7-day combination of PPI plus two antibiotics are summarized in Table 1.[11–34] In total, 24 studies (2342 patients) were included. Ulcer healing in *H. pylori* eradication success was assessed in 1289 patients. Healing rate (weighted mean) was 86% (95% CI, 84–87%) in all patients (both with *H. pylori* eradication success and failure), and it was 95% (95% CI, 94–96%) when only patients with *H. pylori* eradication success were considered. The characteristics of studies included in the meta-analysis comparing the efficacy on ulcer healing of a 7-day combination of PPI plus two antibiotics vs. this same regimen but prolonging the PPI for several more weeks are summarized in Table 2.[12, 23, 25, 26, 32, 33] Six studies identified with the defined search strategy fulfilled the inclusion criteria and contained data for the planned comparison. Overall, 433 patients were treated with 7-day PPI-based triple therapy, and in 429 PPI was prolonged for 2–4 more weeks. The main results of the meta-analysis comparing these two strategies are

Table 2. Characteristics of studies included in the meta-analysis comparing the efficacy on ulcer healing of 7-day combination of a proton pump inhibitor (PPI) plus two antibiotics vs. this same regimen but prolonging the PPI for several more weeks

Author (ref.)	Methods	Ulcer type	Eradication treatment	Additional PPI dose and time (after eradication regimen)	Time at ulcer healing assessment	Q	Ulcer healing rate	
							7-day PPI only	7-day PPI plus prolonging PPI
Labenz *et al.*[25]	Randomized Double-blinded	DU	O 20 mg b.d. C 250 mg b.d. M 400 mg b.d.	O 20 mg o.d. 3 wk.	4 wk.	4	29/29	23/23
Tepes *et al.*[32]	Randomized Double-blinded	DU	O 20 mg b.d. C 500 mg b.d. A 1 g b.d.	O 20 mg o.d. 2 wk.	8 wk.	4	31/35	32/35
Tulassay *et al.*[33]	Randomized Double-blinded	DU	O or E 20 mg b.d. C 500 mg b.d. A 1 g b.d.	O 20 mg o.d. 3 wk.	4 wk.	4	195/214	202/219
Colin *et al.*[12]	Randomized Double-blinded	DU	O 20 mg b.d. C 500 mg b.d. A 1 g b.d.	O 20 mg o.d. 3 wk.	4 wk.	5	58/67	57/64
Marzio *et al.*[26]	Randomized Double-blinded	DU	O 20 mg b.d. C 500 mg b.d. T 500 mg b.d.	O 20 mg o.d. 3 wk.	8 wk.	4	44/53	41/50
Hsu *et al.*[23]	Randomized No double-blind	DU or GU	O 20 mg b.d. C 250 mg b.d. T 500 mg b.d.	O 20 mg o.d. 4 wk.	9 wk.	2	31/35	33/38

Ulcer healing was considered by intention-to-treat analysis.
DU, duodenal ulcer; GU, gastric ulcer; O, omeprazole; E, esomeprazole; C, clarithromycin; A, amoxicillin; M, metronidazole; T, tinidazole; o.d.: once daily; b.d., twice daily; Q, quality score (Jadad scale, from 0 to 5 points, see Methods).

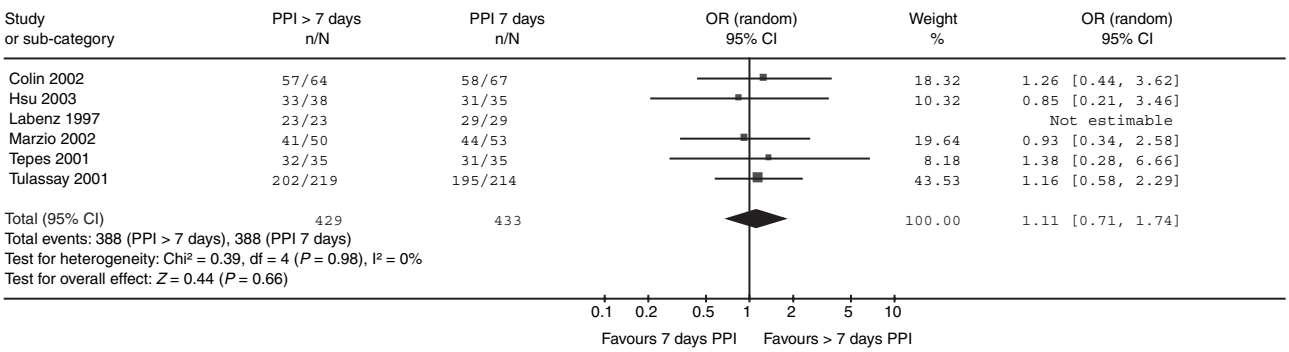

Figure 1. Meta-analysis comparing the efficacy on ulcer healing of 7-day combination of a proton pump inhibitor (PPI) plus two antibiotics vs. this same regimen but prolonging the PPI for several more weeks.[12, 23, 25, 26, 32, 33]

summarized in Figure 1. Mean ulcer healing rates (pooled data) with a 7-day combination of PPI plus two antibiotics was 91% (95% CI, 87–95%) vs. 92% (95% CI, 89–96%) when PPI was prolonged for 2–4 more weeks. The OR for this comparison was 1.11 (95% CI, 0.71–1.74), results being statistically homogeneous (test for heterogeneity chi-square, $P = 0.98$).

Subanalysis

With respect to the ulcer type, 13 studies[12, 13, 15, 18, 21, 25–28, 30–33] evaluated patients with duodenal ulcer only (Table 1), and the ulcer healing rate after 7-day PPI-based triple therapy was 87% (95% CI, 85–89%) overall, and 94% (95% CI, 92–96%) when only patients with *H. pylori* eradication success were considered. Ten studies[11, 14, 16, 17, 19, 20, 23, 24, 29, 34] included both patients with duodenal and/or gastric ulcer disease, and the corresponding healing rates for all patients and for those with *H. pylori* eradication success were 86% (95% CI, 84–88%) and 97% (95% CI, 95–98%). Finally, only one study included exclusively patients with gastric ulcer,[22] and the overall healing rate was 49%. Among the studies included in the meta-analysis,[11–19, 21–34] all but one evaluated patients with duodenal ulcer (this last study[23] included patients with duodenal and/or gastric ulcers together) (Table 2). Subanalysis excluding this study (as separate data for duodenal and for gastric ulcer were not provided in the article), and assessing only duodenal ulcer healing rate, resulted in an OR of 1.14 (95% CI, 0.71–1.84), results being statistically homogeneous ($P = 0.97$). Finally, subanalysis depending on the quality of the study was performed including only studies with a score ≥3 (which has been reported to indicate high quality).[10] When the only study[23] with a quality score <3 (the only one which was not double blinded) was excluded, OR was 1.14 (95% CI, 0.71–1.84).

DISCUSSION

Bismuth therapy was demonstrated to be effective in healing refractory ulcers (resistant to antisecretory drugs) almost 20 years ago,[35, 36] probably due to the effect of bismuth on *H. pylori*. Thereafter, other authors have reported a beneficial effect of *H. pylori* eradication on ulcer healing.[15, 37–41] As previously mentioned, initially, general practice consisted of prescribing PPIs for a further 2–4 weeks after finalizing antibiotic therapy. However, more recently several authors have also achieved very high ulcer healing rates with 'short' eradication therapies using PPI (plus antibiotics) for only 1 week.[11–34] Thus, from our systematic review we have calculated an overall healing rate of 86%, and this figure increased up to 95% when only patients with *H. pylori* eradication success were considered (Table 1). Furthermore, the meta-analysis comparing the efficacy on ulcer healing of a 7-day combination of PPI plus two antibiotics vs. this same regimen but prolonging the PPI for 2–4 more weeks could not demonstrate statistically significant differences (Figure 1),[12, 23, 25, 26, 32, 33] with mean ulcer healing rates of 91 and 92%, respectively (the OR for this comparison was 1.11, with 95% CI from 0.71 to 1.74). Therefore, it may be concluded that 1-week PPI-based treatment for *H. pylori* eradication results in healing of peptic ulcer disease in most patients. This is in contrast to acid suppression alone, as H_2-receptor antagonists take 8 weeks or more and PPIs take 4 weeks to heal duodenal ulcers. Furthermore, ulcer healing rates obtained with 1-week

PPI-based triple regimens are superior to those obtained in trials using omeprazole (20 mg/day) for 2 weeks and are comparable with those obtained in trials that have used this PPI for 4 weeks.[42] In summary, it can be concluded that just 1 week of PPI (that is, the antibiotic administration period recommended in most areas) is enough to obtain ulcer healing in most cases, and continuation of antisecretory drug therapy beyond this time seems actually excessive. Relevant economical savings and simplicity can be inferred from this conclusion.

Studies assessing ulcer healing with 7-day combination of a H_2-blocker or ranitidine bismuth citrate (instead of a PPI) plus two antibiotics, or a PPI plus one antibiotic and bismuth, have shown similar results.[13, 30, 31, 43–46] In this respect, it has been demonstrated that ranitidine bismuth citrate-based triple therapy is an effective treatment for *H. pylori*-related duodenal ulcers. The therapeutic effects of this regimen is comparable to a 1-week course of PPI-based triple therapy not only in eradication rates but also in ulcer healing rates.[31] As an example, in agreement with data obtained with PPI-based treatment, two recent randomized studies have compared 7-day combination of ranitidine bismuth citrate plus antibiotics for only 1 week vs. prolongation of the antisecretor for some weeks more, demonstrating no differences in ulcer healing rates.[44, 45]

A causal relation between *H. pylori* infection and the development of peptic ulcers would be supported if the bacterial infection were treated successfully with antibiotic agents alone. Thus, the demonstration that treatment with an antibiotic only regimen is effective for the healing of peptic ulcer constitutes the strongest evidence that *H. pylori* infection is aetiologically related to peptic ulcer disease. Some studies have shown that antibacterial therapy alone can heal peptic ulcers without acid-suppressing agents.[47–51] Two randomized studies have compared antibiotic treatment alone vs. antibiotic treatment plus a PPI.[48, 51] In a pioneer study, Hosking *et al.*[48] randomized patients with *H. pylori* infection and duodenal ulcer to receive either a 1-week course of bismuth subcitrate, tetracycline and metronidazole, or omeprazole for 4 weeks with the same three-drug regimen for the first week. Duodenal ulcers healed in 92% of the patients taking bismuth, tetracycline and metronidazole compared with 95% taking omeprazole in addition to the three other drugs. Another study where H_2-blockers instead a PPI was prescribed together with antibiotics, also demonstrated that eradication of *H. pylori* with antibiotics alone achieve ulcers healing without the need for an additional antisecretory agent.[52] Nevertheless, Wheeldon *et al.*[34] compared, in a randomized study, once-daily regimens, with and without a PPI, with standard, twice-daily, triple therapy. Ulcer healing after standard therapy (83%) was not significantly better than that after once-daily therapy (73%), but was better than that after therapy without PPI (65%). Finally, some authors have demonstrated that, in patients with *H. pylori* infection and peptic ulcers, 1 week of antibacterial therapy without acid suppression heals the ulcers as well as PPI monotherapy.[53]

Eradication of *H. pylori* favours ulcer healing, which greatly encourages the use of eradication therapy in patients with peptic ulcer disease.[4] Treiber *et al.*[41] demonstrated, in their systematic review, that prolonged treatment with a PPI improves the ulcer healing rate after antimicrobial therapy, but only in those patients who remain *H. pylori*-positive. In agreement with these results, our review of 7-day PPI-based triple regimens showed that, although overall healing rate was already high (86%) when all patients were considered, this figure increase up to 95% when only patients with *H. pylori* eradication success were taken into account; therefore, it seems improbable that prolonging the PPI in this last group of *H. pylori* eradicated patients could increase the already very high ulcer healing rate. On the contrary, as it has been calculated that prolonged treatment with a PPI in patients with *H. pylori* eradication failure improves the ulcer healing rate by about 10%,[41] the therapeutical advantage of this strategy would be very limited: with modern PPI-based triple therapies, eradication rates of approximately 80% have been reported, which means that only 10% of the remaining 20% of *H. pylori* positive patients – that is, only 2% of the total – would benefit from prolonging PPIs after finishing the eradication regimen.

At present, the reason why eradication favours ulcer healing is unknown. It may be a result of histological improvement of the gastric mucosa. Eradication of *H. pylori* is also associated with a decrease in gastrin levels and, possibly, with a decrease in gastric acid output as well (although this is a controversial issue[54]), which could enhance ulcer healing. Finally, *H. pylori* eradication regulates bicarbonate duodenal secretion,[55] which in turn might favour ulcer healing.

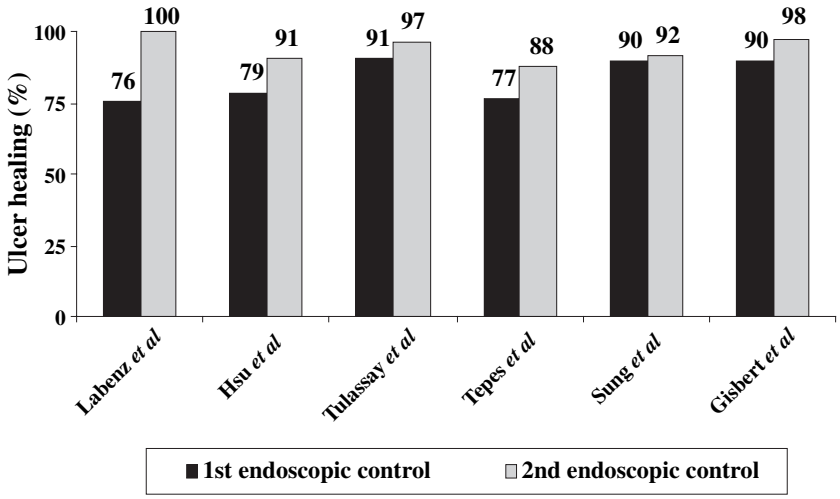

Figure 2. Ulcer healing rate achieved with 1-week proton pump inhibitor-based triple therapy at a first and second control endoscopy.[15, 23, 25, 31–33] 1st control, first endoscopic control after completing eradication treatment; 2nd control, second endoscopic control several week after the first one.

The effect of *H. pylori* eradication on ulcer healing has been evaluated mainly in duodenal ulcer disease. In our review, duodenal ulcer healing rate after 7-day PPI-based triple therapies was 87% overall and 94% in patients with *H. pylori* eradication success (Table 1). In the meta-analysis, all but one study included patients with duodenal ulcer (Table 2), and the subanalysis of these studies did not significatively change the results. Treiber *et al.*,[41] in an exhaustive review of the literature, found that successful *H. pylori* eradication induced a better response in peptic ulcer healing, regardless of diagnosis of duodenal or gastric ulcer. Leodolter *et al.*[3] performed a meta-analysis to compare the efficacy of *H. pylori* eradication on healing rates in *H. pylori*-infected patients with duodenal or gastric ulcer disease, and they concluded that the eradication of the infection cures both types of ulcer, and the cure rates are similar. In the systematic review by Hopkins *et al.*[56] of the effect of eradication of peptic ulcer as a function of its site, an important conclusion was drawn that *H. pylori* eradication can serve as the primary efficacy end-point for healing of active ulcer disease associated with *H. pylori* infection. Bermejo *et al.*[57] studied which factors influence ulcer healing in 230 patients suffering from gastric ulcer and *H. pylori* infection, and treated them with 7-day PPI-based triple therapy; in the multivariate analysis, *H. pylori* eradication was the only variable that correlated with gastric ulcer healing. Finally, some authors have compared, in the same study, ulcer healing rates of duodenal and gastric ulcers after *H. pylori* eradication, and could find no differences between the ulcer types.[14, 24]

Nevertheless, whether 1-week PPI-based triple therapy is sufficient to heal gastric ulcer remains controversial. Although acid suppression is predictive for both types of ulcer, the duration of treatment differs: maintaining the gastric pH above 3 for 18 h out of 24 h healed almost all duodenal ulcers within 4 weeks, but gastric ulcer healing required 8 weeks.[58] General clinical experience shows that gastric ulcers require more time to heal than duodenal ulcers.[58] Lai *et al.*[59] studied the efficacy of a 2-week eradication therapy (with PPI, clarithromycin and amoxicillin) in the healing of *H. pylori*-associated bleeding peptic – gastric and duodenal – ulcers. Ulcer-healing drugs were not continued following completion of the 2-week triple therapy. The multivariate analysis demonstrated that small ulcers (<15 mm) and the presence of duodenal ulcers (as opposite to gastric ulcers) best predicted healing of the peptic ulcers. The superiority of healing in bleeding duodenal ulcers over gastric ulcers may be partly contributed to by the larger ulcer size in patients with bleeding gastric ulcers. In this respect, Higuchi *et al.*[22] showed that, in one subset of gastric ulcers, those measuring ≥1.5 cm, almost no ulcers healed after *H. pylori* eradication alone. In summary, it may be concluded that *H. pylori* eradication favours ulcer healing not only in patients with duodenal ulcer but also with gastric ulcer, indicating that *H. pylori* is the key factor in peptic ulcer disease independent of the ulcer site. However, further randomized clinical trials are needed to clarify whether there is a need for prolongation of therapy with a PPI in all or in some patients with gastric ulcers. In the meantime, it may be suggested that 7-day PPI-based triple therapy might be a standard treatment for smaller gastric ulcers (for example ≤ 1 cm), with additional acid-suppressive therapy being given for larger ulcers at the end of triple therapy.

As previously reviewed, the ulcer healing rate achieved with 1-week PPI-based triple therapy, evaluated at a first control endoscopy (e.g. at 1–2 months), is considerably high, of about 90%. Furthermore, several studies have included a second endoscopic control (e.g. 1–2 months later) and have demonstrated that, without any additional antisecretory treatment after 1-week PPI-based triple therapy, cumulative ulcer healing rate increased up to almost 100% (Figure 2).[15, 23, 25, 31–33] Thus, an explanation for the persistence of the ulcer despite *H. pylori* eradication is that ulcers require a longer period of time to heal in some patients. Most likely, this latency period is necessary to fully obtain the beneficial effect of eradication on ulcer healing in some cases. From these results, it seems that the majority of ulcers which do not heal initially despite *H. pylori* eradication –in itself an uncommon occurrence– will ultimately heal several weeks later without additional therapy.

Finally, another important question is whether prolonged therapy with a PPI has any influence on the symptoms. The 2-week prolonged therapy with the PPI did not have a statistically significant influence on the disease-related symptoms (frequency, type and severity) in a recent study.[32] Other authors also found that the outcome of symptoms, at 4 weeks, was similar in the groups with and without additional prescription of PPI for 21 days after 1-week PPI-based triple therapy.[26, 33] In summary, 1-week PPI-based triple therapy is effective not only to heal the ulcer but also to relief the symptoms. Thus, symptoms generally disappear during this 1-week and prolonged acid suppression does not seem to be essential.

In conclusion, most of the studies reported so far dealing with the treatment of active peptic ulcer in the presence of *H. pylori* infection have a triple therapy schedule with this regimen followed by acid suppression for a further 1–4 weeks. Additional acid inhibition after initial eradication therapy could heal a greater proportion of patients only if bacterial eradication has failed, which only occur in a minority of cases. However, if eradication was successful, there is no further improvement in ulcer healing rates by subsequent acid inhibition. Therefore, in most patients with active uncomplicated peptic ulcer and *H. pylori* infection, prolonging therapy with PPI after a triple therapy for 7 days with a PPI and two antibiotics is not necessary to induce ulcer healing. While this conclusion is supportable in duodenal ulcer, we cannot state with any certainty that the same is true for patients with gastric ulcer, although such patients seem to profit, in general, in the same way. Given the relatively high rate of eradication achieved with the present regimens, and the aforementioned tendency for unhealed ulcers to progress to healing when *H. pylori* has been eradicated, it may be suggested that further acid suppressive therapy could probably be reserved for those patients who are symptomatic following the initial 7 day course of therapy, or those with large, refractory or complicated (e.g. bleeding) ulcers. These patients should probably continue antisecretory therapy until bacterial eradication has been documented.

ACKNOWLEDGEMENT

This study was supported in part by a grant from the Instituto de Salud Carlos III (C03/02).

REFERENCES

1 Malfertheiner P, Megraud F, O'Morain C, *et al.* Current concepts in the management of *Helicobacter pylori* infection – the Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther 2002; 16: 167–80.
2 Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials [see comments]. Am J Gastroenterol 1998; 93: 1409–15.
3 Leodolter A, Kulig M, Brasch H, Meyer-Sabellek W, Willich SN, Malfertheiner P. A meta-analysis comparing eradication, healing and relapse rates in patients with Helicobacter pylori-associated gastric or duodenal ulcer. Aliment Pharmacol Ther 2001; 15: 1949–58.
4 Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: systematic review and economic analysis. Am J Gastroenterol 2004; 99: 1833–55.
5 Buckley M, O'Morain C. *Helicobacter pylori* eradication – a surrogate marker for duodenal ulcer healing. Eur J Gastroenterol Hepatol 1996; 8: 415–6.
6 Bianchi Porro G, Parente F, Lazzaroni M. Short and long term outcome of *Helicobacter pylori* positive resistant duodenal ulcers treated with colloidal bismuth subcitrate plus antibiotics or sucralfate alone [see comments]. Gut 1993; 34: 466–9.
7 Mantzaris GJ, Hatzis A, Tamvakologos G, Petraki K, Spiliades C, Triadaphyllou G. Prospective, randomized, investigator-blind trial of *Helicobacter pylori* infection treatment in patients with refractory duodenal ulcers. Healing and long-term relapse rates. Dig Dis Sci 1993; 38: 1132–6.
8 Lanas AI, Remacha B, Esteva F, Sainz R. Risk factors associated with refractory peptic ulcers [see comments]. Gastroenterology 1995; 109: 1124–33.

9 Williams MP, Pounder RE. What are appropriate end-points for *Helicobacter pylori* eradication in the treatment of duodenal ulcer? Drugs 1998; 56: 1–10.

10 Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1–12.

11 Adamek RJ, Szymanski C, Pfaffenbach B, Opferkuch W, Ricken D, Wegener M. Short-term triple therapy with pantoprazole, clarithromycin and metronidazole for the healing of *Helicobacter pylori* infection. Dtsch Med Wochenschr 1995; 120: 358–60.

12 Colin R. Duodenal ulcer healing with 1-week eradication triple therapy followed, or not, by anti-secretory treatment: a multicentre double-blind placebo-controlled trial. Aliment Pharmacol Ther 2002; 16: 1157–62.

13 Forne M, Viver JM, Esteve M, *et al.* Randomized clinical trial comparing two one-week triple-therapy regimens for the eradication of *Helicobacter pylori* infection and duodenal ulcer healing. Am J Gastroenterol 1998; 93: 35–8.

14 Garcia S, Fuentes J, Ducons JA, Barrera F, Yus C, Gomollon F. Is 1-week treatment for peptic ulcer healing sufficient and safe? [see comments]. Rev Esp Enferm Dig 2000; 92: 5–12.

15 Gisbert JP, Boixeda D, Martin De Argila C, Alvarez Baleriola I, Abraira V, Garcia Plaza A. Unhealed duodenal ulcers despite *Helicobacter pylori* eradication. Scand J Gastroenterol 1997; 32: 643–50.

16 Goh K, Parasakthi N, Cheah P, *et al.* Efficacy of a 1-week pantoprazole triple therapy in eradicating *Helicobacter pylori* in Asian patients [In Process Citation]. J Gastroenterol Hepatol 2000; 15: 910–4.

17 Goh KL, Rosaida MS, Salem O, *et al.* Efficacy of a 1-week rebeprazole triple therapy for eradicating *Helicobacter pylori* and ulcer healing: an ''in-clinical-practice'' study. Chin J Dig Dis 2003; 4: 204–8.

18 Gomollon F, Santolaria S, Ducons JA, Guirao R, Vera J, Montoro M. Does eliminating *Helicobacter pylori* mean the healing of the duodenal ulcer? The results of a prospective study in Spain. Gastroenterol Hepatol 2000; 23: 62–5.

19 Jaup BH, Norrby A. Low dose, short-term triple therapy for cure of *Helicobacter pylori* infection and healing of peptic ulcers. Am J Gastroenterol 1995; 90: 943–5.

20 Jaup BH, Norrby A. Comparison of two low-dose one-week triple therapy regimens with and without metronidazole for cure of H. pylori infection. Aliment Pharmacol Ther 1996; 10: 275–7.

21 Harris AW, Misiewicz JJ, Bardhan KD, *et al.* Incidence of duodenal ulcer healing after 1 week of proton pump inhibitor triple therapy for eradication of *Helicobacter pylori*. The Lansoprazole Helicobacter Study Group. Aliment Pharmacol Ther 1998; 12: 741–5.

22 Higuchi K, Fujiwara Y, Tominaga K, *et al.* Is eradication sufficient to heal gastric ulcers in patients infected with *Helicobacter pylori*? A randomized, controlled, prospective study. Aliment Pharmacol Ther 2003; 17: 111–7.

23 Hsu CC, Lu SN, Changchien CS. One-week low-dose triple therapy without anti-acid treatment has sufficient efficacy on *Helicobacter pylori* eradication and ulcer healing. Hepatogastroenterology 2003; 50: 1731–4.

24 Labenz J, Tillenburg B, Peitz U, *et al.* Ulcer healing through the elimination of *Helicobacter pylori*: is a week of therapy enough? Dtsch Med Wochenschr 1996; 121: 3–7; discussion 7–8.

25 Labenz J, Idstrom JP, Tillenburg B, Peitz U, Adamek RJ, Borsch G. One-week low-dose triple therapy for *Helicobacter pylori* is sufficient for relief from symptoms and healing of duodenal ulcers. Aliment Pharmacol Ther 1997; 11: 89–93.

26 Marzio L, Cellini L, Angelucci D. Triple therapy for 7 days vs. triple therapy for 7 days plus omeprazole for 21 days in treatment of active duodenal ulcer with *Helicobacter pylori* infection. A double blind placebo controlled trial. Dig Liver Dis 2003; 35: 20–3.

27 Schutze K, Hentschel E. Duodenal ulcer healing after 7-day treatment: a pilot study with lansoprazole, amoxicillin and clarithromycin. Z Gastroenterol 1995; 33: 651–3.

28 Schutze K, Hentschel E, Hirschl AM. Effect of omeprazole and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the healing of duodenal ulcer: comparison with a historical control. Hepatogastroenterology 1999; 46: 2358–62.

29 Spinzi GC, Bierti L, Bortoli A, *et al.* Comparison of omeprazole and lansoprazole in short-term triple therapy for *Helicobacter pylori* infection. Aliment Pharmacol Ther 1998; 12: 433–8.

30 Spinzi GC, Boni F, Bortoli A, *et al.* Seven-day triple therapy with ranitidine bismuth citrate or omeprazole and two antibiotics for eradication of *Helicobacter pylori* in duodenal ulcer: a multicentre, randomized, single-blind study. Aliment Pharmacol Ther 2000; 14: 325–30.

31 Sung JJ, Leung WK, Ling TK, *et al.* One-week use of ranitidine bismuth citrate, amoxycillin and clarithromycin for the treatment of *Helicobacter pylori*-related duodenal ulcer. Aliment Pharmacol Ther 1998; 12: 725–30.

32 Tepes B, Krizman I, Gorensek M, Gubina M, Orel I. Is a one-week course of triple anti-*Helicobacter pylori* therapy sufficient to control active duodenal ulcer? Aliment Pharmacol Ther 2001; 15: 1037–45.

33 Tulassay Z, Kryszewski A, Dite P, *et al.* One week of treatment with esomeprazole-based triple therapy eradicates *Helicobacter pylori* and heals patients with duodenal ulcer disease. Eur J Gastroenterol Hepatol 2001; 13: 1457–65.

34 Wheeldon TU, Hoang TT, Phung DC, Bjorkman A, Granstrom M, Sorberg M. *Helicobacter pylori* eradication and peptic ulcer healing: the impact of deleting the proton pump inhibitor and using a once-daily treatment. Aliment Pharmacol Ther 2003; 18: 93–100.

35 Lam SK, Lee NW, Koo J, Hui WM, Fok KH, Ng M. Randomised crossover trial of tripotassium dicitrato bismuthate versus high dose cimetidine for duodenal ulcers resistant to standard dose of cimetidine. Gut 1984; 25: 703–6.

36 Porro GB, Parente F, Lazzaroni M. Tripotassium dicitrato bismuthate (TDB) versus two different dosages of cimetidine in the treatment of resistant duodenal ulcers. Gut 1987; 28: 907–11.

37 Graham DY, Lew GM, Evans DG, Evans DJ Jr, Klein PD. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer

healing. A randomized controlled trial. Ann Intern Med 1991; 115: 266–9.
38 Hosking SW, Ling TK, Yung MY, *et al.* Randomised controlled trial of short term treatment to eradicate *Helicobacter pylori* in patients with duodenal ulcer [see comments]. Bmj 1992; 305: 502–4.
39 Hentschel E, Brandstatter G, Dragosics B, *et al.* Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer [see comments]. N Engl J Med 1993; 328: 308–12.
40 O'Connor HJ, Kanduru C, Bhutta AS, Meehan JM, Feeley KM, Cunnane K. Effect of *Helicobacter pylori* eradication on peptic ulcer healing. Postgrad Med J 1995; 71: 90–3.
41 Treiber G, Lambert JR. The impact of *Helicobacter pylori* eradication on peptic ulcer healing. Am J Gastroenterol 1998; 93: 1080–4.
42 Wilde MI, McTavish D. Omeprazole. An update of its pharmacology and therapeutic use in acid-related disorders. Drugs 1994; 48: 91–132.
43 Dupas JL, Corallo J, Helbert T, Zaim M. Acid suppression therapy is not required after one-week anti-*Helicobacter pylori* triple therapy for duodenal ulcer healing. Gastroenterol Clin Biol 2000; 24: 638–43.
44 Marchi S, Costa F, Bellini M, *et al.* Ranitidine bismuth citrate-based triple therapy for seven days, with or without further anti-secretory therapy, is highly effective in patients with duodenal ulcer and *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 2001; 13: 547–50.
45 Kamberoglou D, Polymeros D, Sanidas I, *et al.* Comparison of 1-week vs. 2- or 4-week therapy regimens with ranitidine bismuth citrate plus two antibiotics for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 2001; 15: 1493–7.
46 Forne M, Viver JM, Espinos JC, Coll I, Tresserra F, Garau J. Impact of colloidal bismuth subnitrate in the eradication rates of *Helicobacter pylori* infection-associated duodenal ulcer using a short treatment regimen with omeprazole and clarithromycin: a randomized study [see comments]. Am J Gastroenterol 1995; 90: 718–21.
47 Zheng ZT, Wang ZY, Chu YX, *et al.* Double-blind short-term trial of furazolidone in peptic ulcer. Lancet 1985; 1: 1048–9.
48 Hosking SW, Ling TK, Chung SC, *et al.* Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment: randomised controlled trial [see comments]. Lancet 1994; 343: 508–10.
49 Sung JJ, Chung SC, Ling TK, *et al.* Antibacterial treatment of gastric ulcers associated with *Helicobacter pylori* [see comments]. N Engl J Med 1995; 332: 139–42.
50 Lam SK, Ching CK, Lai KC, *et al.* Does treatment of *Helicobacter pylori* with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study [see comments]. Gut 1997; 41: 43–8.
51 Ge ZZ, Zhang DZ, Xiao SD, Chen Y, Hu YB. Does eradication of *Helicobacter pylori* alone heal duodenal ulcers? Aliment Pharmacol Ther 2000; 14: 53–8.
52 Massarrat S, Ihm P, Koch HK. Efficacy of tetracycline and metronidazole alone or with ranitidine on the healing of duodenal ulcer and eradication of *Helicobacter pylori*. A randomized controlled multicenter study. Tetra-Metro-Ran Study Group. Arzneimittelforschung 1998; 48: 686–90.
53 Ng EK, Lam YH, Sung JJ, *et al.* Eradication of *Helicobacter pylori* prevents recurrence of ulcer after simple closure of duodenal ulcer perforation: randomized controlled trial [see comments]. Ann Surg 2000; 231: 153–8.
54 el-Omar EM, Penman ID, Ardill JE, Chittajallu RS, Howie C, McColl KE. *Helicobacter pylori* infection and abnormalities of acid secretion in patients with duodenal ulcer disease [see comments]. Gastroenterology 1995; 109: 681–91.
55 Hogan DL, Rapier RC, Dreilinger A, *et al.* Duodenal bicarbonate secretion: eradication of *Helicobacter pylori* and duodenal structure and function in humans [see comments]. Gastroenterology 1996; 110: 705–16.
56 Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996; 110: 1244–52.
57 Bermejo F, Boixeda D, Martin De Argila C, *et al.* Healing of *Helicobacter pylori* gastric ulcers: only eradication matters. Rev Esp Enferm Dig 2003; 95: 621–4.
58 Hunt RH, Cederberg C, Dent J, *et al.* Optimizing acid suppression for treatment of acid-related diseases. Dig Dis Sci 1995; 40: 24S–49S.
59 Lai KC, Hui WM, Wong BC, Hu WH, Lam SK. Ulcer-healing drugs are required after eradication of *Helicobacter pylori* in patients with gastric ulcer but not duodenal ulcer haemorrhage. Aliment Pharmacol Ther 2000; 14: 1071–6.