How can the current strategies for *Helicobacter pylori* eradication therapy be improved?

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BACKGROUND: The use of *Helicobacter pylori* eradication therapy is advocated in an increasing variety of situations. It is therefore important to optimise current strategies to eradicate *H pylori* infection.
OBJECTIVES: To define the optimum dosage, drugs and duration of proton pump inhibitor (PPI) triple therapy.
METHODS: A review of the literature was performed to identify randomized controlled trials and systematic reviews addressing these issues.
RESULTS: In PPI, amoxicillin and clarithromycin (PAC) based regimens, twice daily PPI gave optimal eradication rates (relative risk reduction [RRR] compared with once daily = 7%; 95% CI 2% to 12%), but in PPI, clarithromycin and metronidazole (PCM) based regimens there was no difference (RRR = 2%; 95% CI –7% to 10%). Omeprazole and lansoprazole-containing triple therapies achieved similar eradication rates, but rabeprazole appeared superior to omeprazole (RRR = 8%; 95% CI 2% to 14%). The optimum clarithromycin dose in a PAC regimen was 500 mg twice daily (RRR = 11%; 95% CI = 3% to 18%), but 250mg twice daily in a PCM regimen (RRR = 2%; 95% CI –4% to 7%). Eradication rates were lower with a seven day regimen compared with fourteen (RRR = 12%; 95% CI 7% to 17%). Overall there was no difference between a PAC and a PCM regimen (RRR = 0%; 95% CI –3% to 3%).
CONCLUSIONS: PAC and PCM regimens are equally effective if used optimally, though PCM is cheaper. The eradication regimen and its duration should be tailored according to the clinical situation.

Key Words: *Clarithromycin; Eradication;* Helicobacter pylori*; Meta-analysis; Proton pump inhibitor*

Comment améliorer les stratégies actuelles relatives au traitement d'éradication du *Helicobacter pylori*?

HISTORIQUE : Le recours au traitement d'éradication du *Helicobacter pylori* est préconisé dans un nombre croissant de situations. Il est donc important d'optimiser les stratégies actuelles visant à éradiquer les infections à *H pylori*.
OBJECTIFS : Définir la dose optimale, les médicaments et la durée de la trithérapie aux inhibiteurs de la pompe à protons (IPP).
MÉTHODOLOGIE : Une analyse bibliographique a été exécutée pour repérer les essais aléatoires et contrôlés et un examen systématique a porté sur ces enjeux.
RÉSULTATS : Selon le schéma thérapeutique d'IPP, d'amoxicilline et de clarythromycine (IAC), une dose d'IPP deux fois par jour assurait le taux d'éradication optimal (la réduction du risque relatif [RRR] par rapport à une dose quotidienne s'élevait à 7 %; 95 % IC 2% à 12 %), mais en cas de schéma thérapeutique d'IPP, de clarithromycine et de métronidazole (ICM), on ne remarquait aucune différence (RRR 2 %; 95 % IC –7 % à 10 %). Les trithérapies contenant de l'oméprazole et du lansoprazole permettaient d'obtenir des taux d'éradication similaires, mais le rabéprazole semblait supérieur à l'oméprazole (RRR 8 %, 98 % IC 2 % à 14 %). La dose optimale de clarithromycine dans un schéma thérapeutique d'IAC s'établissait à 500 mg deux fois par jour (RRR 11 %; 95 % IC 3 % à 18 %), mais à 250 mg deux fois par jour dans un schéma thérapeutique d'ICM (RRR 2 %; 95 % IC –4 % à 7 %). Les taux d'éradication étaient plus faibles après un schéma thérapeutique de sept jours plutôt que de 14 jours (RRR 12 %; 95 % IC 7 % à 17 %). Dans l'ensemble, on ne remarquait aucune différence entre un schéma thérapeutique d'IAC et d'ICM (RRR 0 %; 95 % IC –3 % à 3 %).
CONCLUSIONS : Les schémas thérapeutiques d'IAC et d'ICM sont tout aussi efficaces s'ils sont utilisés de façon optimale, bien que l'ICM coûte moins cher. Le schéma thérapeutique d'éradication et sa durée devraient être adaptés à la situation clinique.

Eradication therapy for *Helicobacter pylori* infection has become an important weapon in the clinician's armoury against dyspepsia. The European *Helicobacter pylori* Study Group (EHPSG) suggests that *H pylori* eradication is strongly recommended for patients with peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, atrophic gastritis, postgastric cancer resection, patients with a first-degree relative with gastric cancer and as part of a test and treat strategy (1). The Maastricht 2-2000 consensus also suggested *H pylori* eradication is advisable for patients with nonulcer dyspepsia, long term acid suppression and before nonsteroidal anti-inflammatory drug therapy (1). With such a variety of indications, it is important to optimize current strategies to eradicate *H pylori* infection.

Trials indicate that clarithromycin-based proton pump inhibitor (PPI) triple therapies are the most effective regimens for the treatment of *H pylori* infection (2,3). A systematic review (4) reported that ranitidine bismuth citrate triple therapy regimens are as effective as their PPI counterparts in eradicating *H pylori*, but because PPI-based triple therapies are more widely used they are the focus of the present review. The aims of the present paper are to address the optimum doses of the drugs used in PPI-based clarithromycin triple therapies to reach conclusions as to the optimal regimens. Strategies that could improve on these therapies using existing antibiotics will also be explored.

OPTIMUM DOSE AND DURATION OF PPI IN CLARITHROMYCIN-BASED THERAPY

Optimum dose of PPI

The dose of PPI required in amoxycillin dual therapy is important, with increasing acid suppression leading to greater efficacy (5). A review and meta-analysis of the literature was performed to evaluate whether the dose of PPI was also important in clarithromycin-

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based triple therapies. Another systematic review in this area that provided further data was found (6). There were 12 randomized controlled trials (RCTs) (7-16) in 2186 patients evaluating single versus double standard dose PPI in clarithromycin and amoxycillin (PAC) regimens. There was a 7% RR reduction (RRR) (95% CI 2% to 12%) of *H pylori* cure in patients randomly assigned to single dose PPI in previous RCTs (Figure 1). Double dose PPI therapy is therefore optimal in PAC regimens (number needed to treat [NNT] was 18; 95% CI 11 to 64).

In three RCTs (17-19), 378 patients were evaluated with single versus double standard dose PPI in clarithromycin and metronidazole (PCM) regimens. There was no statistically significant difference between single versus double dose PPI therapy in PCM regimens (RRR 2%; 95% CI –7% to 10%) (Figure 2). The number of patients evaluated in PCM trials was less than in PAC trials and, therefore, the power of this meta-analysis is limited. Nevertheless, the available data suggest that single dose PPI therapy is sufficient for PCM triple therapy.

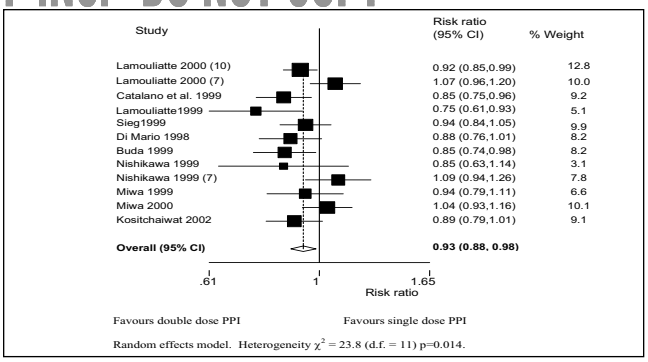

Figure 1) *Randomized controlled trials of single versus double dose proton pump inhibitor (PPI) in PPI with clarithromycin and amoxycillin regimens. df Degrees of freedom*

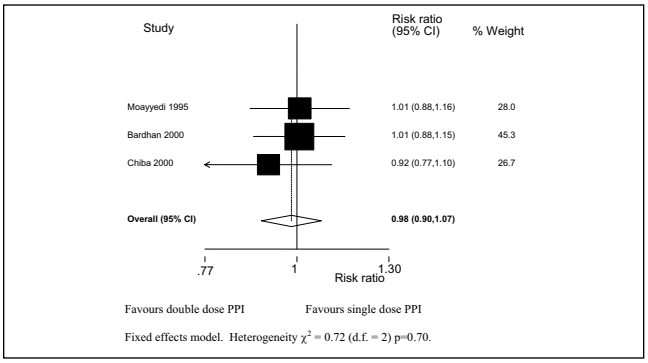

Figure 2) *Randomized controlled trials of single versus double dose proton pump inhibitor (PPI) in PPI with clarithromycin and metronidazole regimens. df Degrees of freedom*

Optimum PPI

A meta-analysis of 10 RCTs performed in 2001 (20), evaluating a total of 1348 patients, showed that there was no significant difference between omeprazole and lansoprazole- containing triple therapies of seven days or more.

However, five RCTs (16,21-24) evaluating 934 patients were found that compared the equivalent doses of rabeprazole and omeprazole in PAC regimens. Meta-analysis of these trials suggests that rabeprazole is superior to omeprazole (RRR 8%, 95% CI 2% to 14%; NNT 16, 95% CI 9 to 65) (Figure 3). With regard to the use of rabeprazole in PCM regimens, there was only one trial comparing it to an omeprazole-containing regimen, and that trial showed no significant difference between the two regimens (22). There was insufficient evidence to allow any comparison between pantoprazole and the other PPIs to be made.

Optimum dose of clarithromycin

The question of the optimum dose of clarithromycin has already been the subject of a systematic review published in 1999 (25). At that time, there were four trials, evaluating a total of 385 patients, comparing clarithromycin 250 mg with clarithromycin 500 mg in a PAC regimen. Meta-analysis suggested that the higher dose of clarithromycin was optimal (RRR 11%, 95% CI 3% to 18%; NNT 11, 95% CI7 to 42) (20). There were also four trials, evaluating a total of 642 patients, comparing 250 mg with 500 mg of clarithromycin in a PCM regimen. Doubling the dose of clarithromycin had no statistically significant effect on eradication rates (RRR 2%; 95% CI –4% to 7%) (20) and a dose of 250 mg has, therefore, been recommended (1).

Since this review, another RCT was identified (26) that shows a benefit in favour of 250 mg of clarithromycin in a PAC regimen. If this trial is included in the meta-analysis, the results become more heterogeneous and the overall effect of increasing the dose of clarithromycin in a PAC regimen is not statistically significant. It is difficult to explain why a lower dose of clarithromycin would be superior in eradicating *H pylori* infection, and the balance of evidence still suggests that the higher dose of clarithromycin should be recommended when included in PAC regimens.

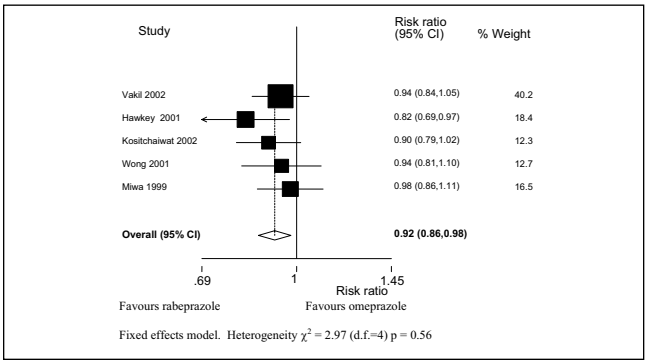

Figure 3) *Randomized controlled trials of rabeprazole versus omeprazole in proton pump inhibitor with clarithromycin and amoxycillin regimens. df Degrees of freedom*

Optimum regimen

The data suggest that the optimum PAC regimen is one that contains a PPI, clarithromycin 500 mg and amoxycillin 1 g, all given twice daily, whereas the optimum PCM regimen is PPI once daily with clarithromycin 250 mg and metronidazole 400 mg twice daily for seven days. A previous systematic review (20) evaluating RCTs that compared these two optimal regimens has been updated. There were 19 trials (26-44) comparing the optimum regimens of PAC to PCM in 3426 patients, and there was no statistically significant difference in eradication rates (RRR 0%, 95% CI –3% to 3%). There was also no statistically significant heterogeneity between trials (Figure 4). There was some variation in trial results, but this could be explained by smaller

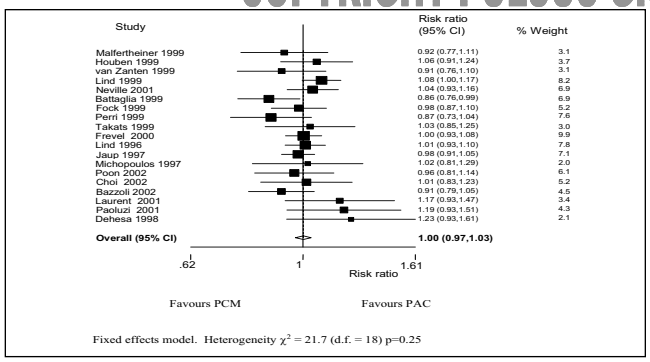

Figure 4) *Randomized controlled trials comparing optimal proton pump inhibitor (PPI), clarithromycin and metronidazole regimens with PPI, clarithromycin and amoxycillin regimens. df Degrees of freedom*

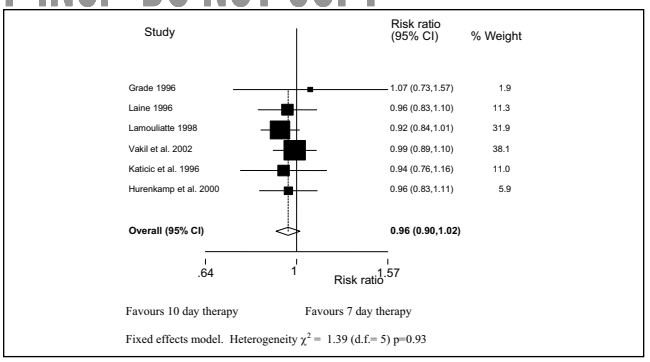

Figure 6) *Randomized controlled trials comparing 10- with seven-day proton pump inhibitor triple therapy. df Degrees of freedom*

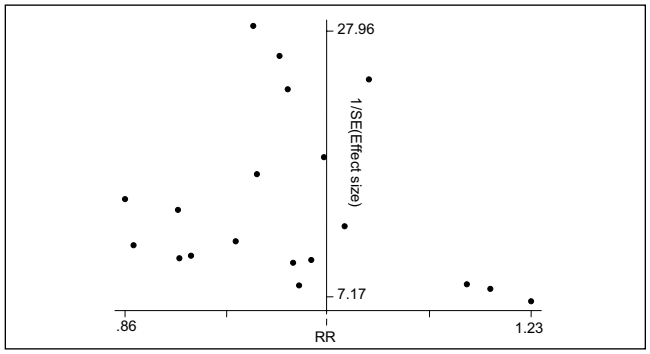

Figure 5) *Funnel plot of randomized controlled trials comparing proton pump inhibitor (PPI), clarithromycin and metronidazole regimens with PPI, clarithromycin and amoxycillin regimens.*

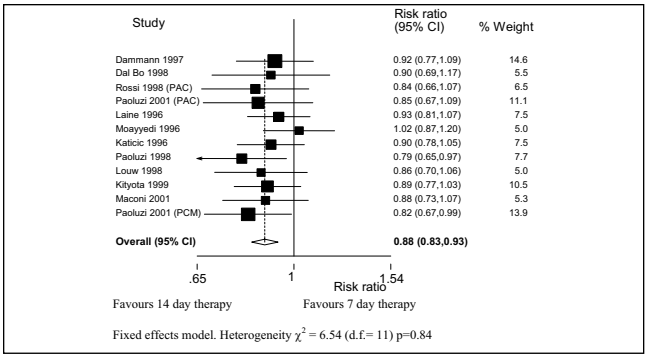

Figure 7) *Randomized controlled trials comparing 14- with seven-day proton pump inhibitor triple therapy. df Degrees of freedom*

trials giving greater variability than larger trials (Figure 5). The finding that there is no difference in efficacy between optimal PAC and PCM regimens is unexpected, because three meta-analyses have suggested that PCM is approximately 20% less effective against metronidazole-resistant strains of *H pylori* (45-47). It is unlikely that all trials had a low prevalence of resistant strains and the number of patients evaluated gives the power to detect even small differences in efficacy between the two regimens (RRR 0%; 95% CI –3% to 3%). Furthermore, there was no significant heterogeneity between the trials, yet many were from different countries with a different prevalence of *H pylori* metronidazole resistance. Again, the number of patients evaluated gives excessive power for detecting heterogeneity between studies and it is surprising that none was found. These data suggest that PCM may be more effective than PAC in metronidazole-sensitive *H pylori* strains and that the impact of metronidazole resistance may not be as marked as observational studies suggest.

STRATEGIES TO IMPROVE EXISTING REGIMENS

Optimum duration of treatment

The most obvious strategy to improve the efficacy of clarithromycin-based PPI triple therapy is to increase the length of therapy. Indeed, American guidelines recommend 10 days of therapy, while European guidelines suggest that seven days is sufficient {1,48}. Shortening the duration of triple therapy to less than seven days has been shown to have a deleterious effect on eradication rates (23,48).

A previous systematic review and meta-analysis (49) was updated and reanalyzed to examine the question of optimum duration of treatment. There were six RCTs (7,21,50-53) evaluating 992 patients that compared seven and 10 days of clarithromycin-based PPI triple therapy. There was a statistically nonsignificant trend for a reduction in *H pylori* cure for seven-day compared with 10-day therapy (RRR 4%; 95% CI –2% to 10%) (Figure 6). Twelve trials (43,51,52,54-60) evaluating 1592 patients that compared seven- with 14-day PPI triple therapy were also identified. Seven days of therapy was significantly less likely to cure *H pylori* infection (RRR 12%, 95% CI 7% to 17%; NNT 12, 95% CI 9 to 21) (Figure 7). These data combine PAC and PCM regimens, but the longer duration therapy was still significantly more effective when these two regimens were considered separately. Present evidence, therefore, suggests that increasing the length of therapy to two weeks will improve eradication rates.

New approaches using existing antibiotics

A recent trial performed in Italy (61) compared a novel 10-day eradication regimen, in the form of five days of rabeprazole 20 mg and amoxycillin 1 g twice daily followed by five days of rabeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg twice daily, with a standard seven-day PAC regimen in 1099 *H pylori*-positive patients. *H pylori* was eradicated in 378 of 399 patients (95%) allocated to the 10-day therapy compared with 301 of 397 patients (76%) given seven days of PAC. This is an interesting finding, but the regimen also needs to be compared with a standard PCM regimen and further trials are needed to ensure that these results can be replicated in other centres.

CONCLUSIONS

The optimum *H pylori* eradication regimen is still the subject of intensive research, with the results of many RCTs being published each year. The Cochrane collaboration (62) is conducting a systematic review that will hopefully give definitive answers as to the most effective therapy. This publication is eagerly awaited but until then a picture appears to be emerging. PAC and PCM are equally effective but the latter requires a lower dose of PPI and clarithromycin. PCM is, therefore, less expensive than PAC and is the most cost effective option. However, the EHPSG guidelines prefer the combination of PAC to be used as first-line treatment (1). The reason for this is that if PAC fails, the second-line treatment of quadruple therapy with PPI, bismuth, metronidazole and tetracycline involves treatment of the patient with antibiotics that they have not previously received. The overall success rate for this strategy could theoretically be as high as 98% (63), whereas if PCM fails as first-line treatment the second-line approach would be PPI and amoxycillin dual therapy, giving an overall theoretical eradication rate of 95% (20).

There can be no generic recommendation for an eradication regimen that should be applied to all cases of *H pylori* infection. Each clinical situation should be considered separately and, using the information available, the best decision for the treatment of that patient should be made. In a 'test and treat' strategy for the management of dyspepsia and when *H pylori* eradication is being used to treat nonulcer dyspepsia, PCM should be used. This is because the gains from *H pylori* eradication are relatively small (64) and, therefore, the cheapest strategy will be the most cost effective (20). In other cases such as peptic ulcer disease and MALT lymphoma, where the evidence suggests that eradication carries a more definite advantage, PAC should be used, and may be more effective if the duration of therapy is 14 days and the possibility that rabeprazole may be more effective in this regimen deserves further consideration.

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