Review Article

THAI J GASTROENTEROL 2010
Vol. 11 No. 3
Sept. - Dec. 2010

Novel *Helicobacter pylori* Eradication Regimen

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Helicobacter pylori was known as the major cause of peptic ulcer, atrophic gastritis and a definite risk factor for gastric cancer. Early approved therapies such as dual therapy with a PPI plus amoxicillin or a PPI plus clarithromycin were quickly abandoned if they failed to provide consistent cure rates of 85% or greater. By contrast, triple therapies consisting of an anti-secretory drug plus amoxicillin and clarithromycin, amoxicillin and metronidazole, or clarithromycin and metronidazole were embraced as they seemed to provide consistent cure rates of at least 90%[1,2].

Recommended novel treatment[1]

By the fact that *H. pylori* eradication with the triple therapy is declining, with increased clarithromycin and metronidazole-resistance strains, a number of recent reviews focus on seeking the novel treatments including;

1. Bismuth-containing quadruple therapy

Quadruple therapy consists of a bismuth salt, tetracycline HCl, metronidazole/tinidazole, and a PPI given three or four times daily. In most countries one should consider that more than 10% of the patients will

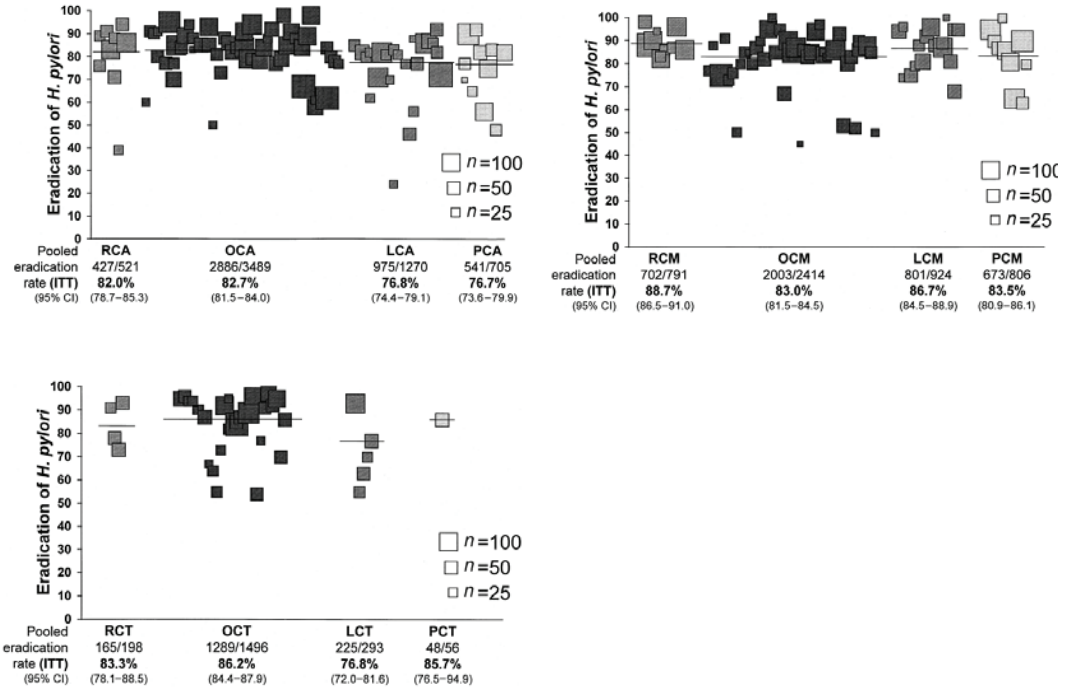

Figure 1.

From: Pikin GA, Williamson R, Wood JR. Review article: one-week clarithromycin triple therapy regimens for eradication of *Helicobacter pylori*. Aliment Pharmacol Ther 1998;12:823-37.

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have metronidazole resistant *H. pylori* and thus the dose of metronidazole should be approximately 1,500 mg and the duration should be 14 days. However, this therapy can only be used in countries were bismuth is available[1]. A recent systematic review and meta-analysis of *H. pylori* eradication rate with quadruple and triple therapies, showed similar results, 78.3% and 77% respectively. The similar eradication rates were maintained in subgroup analyses by location, duration, and treatment population. This analysis also confirms that there is no difference in compliance rate or the incidence of treatment-associated side effects between quadruple and clarithromycin triple therapy[3].

2. Sequential therapy

Sequential therapy was originally described as a 10 day therapy in which the first 5 days consisted of a dual therapy with a PPI and amoxicillin given b.i.d., followed by a triple therapy consisting of PPI, clarithromycin and tinidazole/metronidazole b.i.d. to complete 10 days. The sequential treatment achieved a higher eradication rate compared with PPI-based treatment. First, this may be associated with the usage of 3 different antibiotics in each patient instead of 2. Second, the suppression of bacterial load with PPI and amoxicillin may improve the response to the subsequent short course of triple treatment that a low bacterial load is associated with a higher eradication rate after triple treatment[1,4].

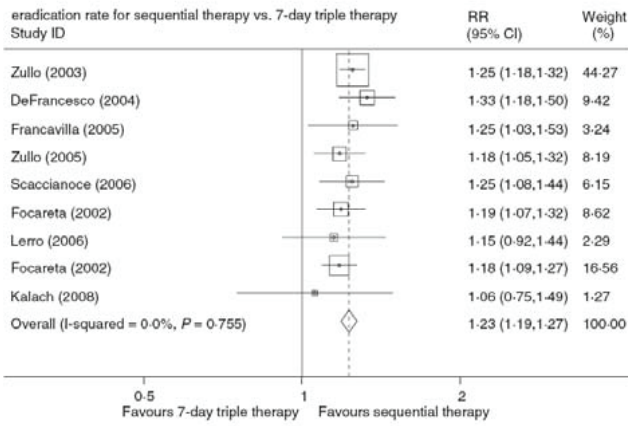

Figure 2. A total of 2883 participants (1338 for sequential regimen and 1545 for standard triple regimens) were enrolled in the 11 included studies. From: Sequential therapy vs. standard triple therapies for *Helicobacter pylori* infection: a meta-analysis. J Clin Pharm and Ther 2009;34:41-53.

3. Concomitant therapy

Concomitant therapy was introduced before sequential therapy, it consists of all four drugs (the PPI, clarithromycin, metronidazole/tinidazole, and amoxicillin) being given b.i.d.. The duration has ranged from 3 to 7 days and it has resulted in good results similar to those obtained with sequential therapy. The percent of cure rate in sequential therapy (n = 1805) for 10 days is 93.4% and in concomitant therapy (n = 715) ranging from 3 to 7 days is 91.7%[1].

4. High dose dual therapy

High dose dual therapy that 80 mg of omeprazole given every 12 hours or PPI dosing every 6 h plus amoxicillin therapy have also proven successful depended on the CYP2C19 genotype status[1,5]. Ninety-seven patients with gastritis and *H. pylori* infection completed the dual therapy with 10 mg of rabeprazole b.i.d. and 500 mg of amoxicillin t.i.d. for 2 weeks. There were 33 homozygous extensive metabolizers (homEM), 48 heterozygous extensive metabolizers (hetEM), and 16 poor metabolizers (PM). Cure of *H. pylori* infection was achieved in 79 of the 97 patients (81.4%, 95%CI = 71.9-88.7). Significant differences in cure rates among the homEM, hetEM, and PM groups were observed; 60.6% (95%CI = 42.1-77.3), 91.7% (95%CI = 80.0-97.7), and 93.8% (95%CI = 69.8-99.8), respectively ($p = 0.0007$)[5]. The dual PPI and amoxicillin component with standard doses for two weeks is expected to provide a cure rate of approximately 50%. Higher and more frequent dosing would be expected to raise the base and thus the overall success[1].

5. New or alternative drugs

Fluoroquinolones, furazolidone, rifabutin and other possibilities have the potential to be modified with new or alternative drugs. The meta-analyses have shown, short-duration fluoroquinolone results (e.g. 7 days) were significantly inferior (e.g. Grade F) to treatment for 10 days, which itself only produced a Grade C result (85-89% ITT cure rate)[6]. Unfortunately, fluoroquinolone resistance has been rapidly increasing and these drugs will probably be rendered useless before an effective protocol is devised. Rifabutin and furazolidone are especially useful for patients who have experienced multiple treatment failures because these antibiotics are rarely used and, therefore, resistance to them is unlikely. Like bismuth, furazolidone is not available in many countries.[1]

6. Probiotics

In vitro studies demonstrated an inhibitory

activity of probiotics on *H. pylori* growth and that this effect is extremely strain specific. Available data in children indicate that probiotics seems to be efficacious for the prevention of antibiotic associated side-effects, and might be of help for the prevention of *H. pylori* complications by decreasing *H. pylori* density and gastritis, and for the prevention of *H. pylori* colonization or re-infection by inhibiting adhesion to gastric epithelial cells. There is no clear evidence that probiotics may increase the *H. pylori* eradication rate[7].

Well-designed clinical studies and experimental animal models have demonstrated that supernatant from *L. johnsonii La1* culture of the strain inhibits the growth of *H. pylori* both in vitro and in vivo[8]. *H. pylori* infection and chronic gastritis can be down regulated by the daily consumption of yoghurt containing selected strains of *L. johnsonii*[9]. 53 subjects infected with *H. pylori* were randomized to receive either La1 or a placebo 180 ml twice a day for 3 weeks. All the subjects also received clarithromycin 500 mg twice a day during the last two weeks of acidified milk therapy. After the end of the treatment, there were diminished the density of *H. pylori* colonization, inflammation of the antrum and the activity of the inflammation in both the antrum and the corpus[9].

Thirty-one subjects infected with *H. pylori* ingested yoghurt containing LG21 daily for an 8-week period. The density of *H. pylori* colonization of the gastric mucosa and gastric inflammation were determined by the urea breath test and serum pepsinogen I and II determination. LG21 was effective in both suppressing *H. pylori* and reducing gastric mucosal inflammation[10].

7. Herbal medicines (Plaunotol, Curcumin and Aloe vera)

Plaunotol, a cytoprotective anti-ulcer agent, has antibacterial activity against *H. pylori*. Tetsufumi Koga 2002, in a *H. pylori* induced gastritis mouse model, the plaunotol-clarithromycin and plaunotol-amoxicillin combinations both exhibited synergic effects, which allowed the effective dose of clarithromycin to be reduced when co-administered with plaunotol[11]. Makoto Sasaki 2007, Mongolian gerbils model infected with clarithromycin-resistant strains, the plaunotol (40 mg/kg) and clarithromycin (66.6 mg/kg) combination exhibited synergistic effects, which neither of them showed bactericidal effects alone[12].

Curcumin (diferuloylmethane), an active constituent of Curcuma longa, has potential anti-inflammatory properties. Curcumin is also a potent antibacterial agent against *H. pylori* in in vitro study although curcumin did not eradicate *H. pylori* in *H. pylori*-infected patients[13]. Ronita De 2009, *H. pylori* infected mice, which treated with 7 day-curcumin after *H. pylori* infection for 2 weeks, compared with a control group, 3 week- *H. pylori* infection. The curcumin treated group showed completely eliminated *H. pylori* from mouse stomach by PCR using DNA isolated method. By histological analysis, mouse gastric tissues were restored to almost normal after curcumin treatment[14]. Thong-Ngam D 2010, *H. pylori* infected rats increased macromolecular leakage from gastric mucosal PCVs, serum VEGF level, and gastric epithelial NF-κB p65 expression. Curcumin treatment can decrease the macromolecular leakage from gastric mucosa PCVs through the suppression of NF-κB activation in gastric epithelial cells[15].

Aloe vera, one of the most widely used healing plants, has anti-inflammatory, cytoprotective, healing and mucus stimulatory effects. In the experiment that observe the leukocyte activity in gastric microcirculation using intravital fluorescence microscope by using acridine orange to label leukocyte. The twice daily treatment of Aloe vera (400 mg/kg BW/day) could significantly reduce the leukocyte-endothelium interaction and changes through the reduction of pro-inflammatory cytokine[16].

In conclusion: The novel therapeutic regimens such as quadruple therapy, sequential therapy, concomitant therapy, high dose dual therapy, the alternative non-antibiotic treatments, *plaunotol, curcumin, Aloe vera* and probiotics would become the focus of attention for further experiments.

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