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A Randomized Controlled Study Comparing Reverse Hybrid Therapy and Standard Triple Therapy for *Helicobacter pylori* Infection

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Abstract: Reverse hybrid therapy is an 1-step 2-phase treatment for *Helicobacter pylori* (*H. pylori*) infection with less cost than standard triple therapy. We conducted a randomized, controlled study to compare the efficacies of standard triple therapy and reverse hybrid therapy in the treatment of *H. pylori* infection.

From October 2012 to March 2015, consecutive *H. pylori*-infected subjects were randomly allocated to receive either a reverse hybrid therapy (pantoprazole plus amoxicillin for 12 days and clarithromycin plus metronidazole for the initial 7 days) or a standard triple therapy (pantoprazole plus amoxicillin and clarithromycin for 12 days). *H. pylori* status was assessed 6 weeks after treatment. Additionally, antibiotic resistances and host *CYP2C19* genotypes were examined and analyzed.

A total of 440 *H. pylori*-infected patients were randomly assigned to receive either a reverse hybrid (n = 220) or a standard triple therapy (n = 220). The reverse hybrid group had a higher eradication rate than standard triple group either by intention-to-treat (93.6% vs. 86.8%; $P = 0.016$) or per-protocol analysis (95.7% vs. 88.3%; $P = 0.005$). The 2 patient groups exhibited similar frequencies of overall adverse events (14.1% vs. 9.5%) and drug compliance (96.8% vs. 98.6%). Clarithromycin resistance was an independent risk factor predicting eradication failure in standard triple group ($P < 0.001$), but not in reverse hybrid group. *CYP2C19* genotypes did not affect the eradication rates in both groups.

Reverse hybrid therapy can be considered for first-line treatment of *H. pylori* infection since the new therapy achieves a higher eradication rate than standard triple therapy with similar tolerability and less pharmaceutical cost.

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Abbreviations: bd = twice a day, CI = confidence interval, *H. pylori* = *Helicobacter pylori*, hetEM = heterogeneous extensive metabolizer, homEM = homogeneous extensive metabolizer, ITT = intention-to-treat, MALToma = mucosa-associated lymphoid tissue lymphoma, PM = poor metabolizer, PP = per-protocol, PPI = proton pump inhibitor.

INTRODUCTION

Helicobacter pylori (H. pylori) infection is well recognized as the leading cause of chronic gastritis, peptic ulcer disease, and gastric cancer.[1–5] Currently, *H. pylori* treatment remains a challenge for physicians as antimicrobial resistance has continued to increase worldwide. Although standard triple therapy has been recommended as the first-line therapy in many guidelines,[6–9] its eradication rate has decreased to unacceptable level in most parts of the world.[10–15] The growing treatment failure rate is generally attributed to an increasing prevalence of resistance to clarithromycin, a basic component of standard triple therapy.[10–12,15] An updated consensus report[8] has therefore proposed a bismuth-containing quadruple therapy or non-bismuth quadruple therapy (sequential or concomitant therapy)[16–18] as first-line treatment in settings with clarithromycin resistance rates greater than 15% to 20%. Although levofloxacin-based triple therapy can achieved a high eradication rate in populations with clarithromycin resistance greater than 20% and quinolone resistance less than 10%,[19] it is not generally recommended as a first-line therapy on concerns of the rapid development of resistant strains.

Hybrid (dual–quadruple) therapy developed by Hsu et al. consists of a proton pump inhibitor (PPI) and amoxicillin for 14 days with addition of clarithromycin and metronidazole for the final 7 days.[20] In its pilot study, hybrid therapy generated excellent eradication rates of 99% and 97% according to per-protocol (PP) and intention-to-treat (ITT) analyses. Subsequent randomized trials demonstrated that hybrid regimens were either comparable with or more effective than sequential therapies.[21–23] Recently, a large multicenter randomized trial also showed that both 14-day hybrid and 14-day concomitant therapies cured more than 90% of the patients with *H. pylori* infection in areas with high clarithromycin and metronidazole

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