中文題目：應用基因型抗藥性選擇幽門螺旋桿菌第三線相繼式治療藥物之療效--一項國內多中心之臨床試驗

英文題目：The efficacy of genotypic resistance guided sequential therapy in the third line treatment for *Helicobacter pylori* infection- A multicenter clinical trial

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Background: Sequential therapy containing clarithromycin has been reported to be more effective than triple therapy in the first line therapy. Susceptibility-guided therapy was recommended for refractory *Helicobacter pylori (H. pylori)* infection after two treatment failures. However, culture and susceptibility test are time consuming and are not widely available. Point mutations in the 23S ribosomal RNA (23S rRNA) and *gyrase* A (*gyr*A) genes have been shown to be associated with clarithromycin and levofloxacin resistance, respectively. Point mutations at 23S rRNA and gyrA also correlated with eradication outcomes after clarithromycin-based and levofloxacin-based triple therapies, respectively. However, whether the genotypic resistance could be used to guide the selection of antibiotics in the third line treatment has not been reported. Therefore, we aimed to assess the efficacy and tolerability of genotypic resistance guided sequential therapy in the third line treatment.

Materials and Methods: This single arm, multicenter clinical trial was conducted since April, 2009 in Taiwan. Patients who failed from at least two treatments for *H. pylori* infection were eligible. All eligible patients underwent upper endoscopy and gastric biopsy. Genotypic resistance for 23S rRNA and gyrA mutations was determined on biopsy specimens and *H. pylori* strains. Phenotypic resistance was also determined by Agar dilution test for correlation if strains were available. Patients were treated with sequential therapy containing esomeprazole 40mg and amoxicillin 1g for the first 7 days, followed by esomeprazole 40mg and metronidazole 500mg plus either (1) clarithromycin 500mg, or (2) levofloxacin 250mg, or (3) tetracycline 500mg for another 7 days (all drugs were given twice daily) according to genotypic resistance determined on biopsy specimens or strains. In the absence of 23S rRNA mutation, clarithromycin-based sequential therapy would be given. In the presence of the 23S rRNA mutation, levofloxacin-based sequential therapy would be given in the absence of gyrA mutation. In the presence of both 23S rRNA and gyrA mutation, tetracycline-based sequential therapy would be given empirically since the prevalence of tetracycline resistance was low (less than 5% according to previous reports). After third line treatment, *H. pylori* status was determined by ^{13}C-UBT at least 6 weeks after completion of treatment.

Results: A total of 115 patients had been enrolled and the results were available for analysis in 99 patients up to Oct 5, 2011. Genotypic resistance determined on biopsy specimens correlated well with phenotypic resistance for both clarithromycin (Kapp=0.875, $p<0.001$) and

levofloxacin (Kappa=0.901, p<0.001). The prevalence of resistance for clarithromycin, levofloxacin, tetracycline, metronidazole, and amoxicillin were 86.8%, 42.6%, 3%, 52.9%, and 7.4%, respectively. Two patients were excluded from per protocol (PP) analysis (one withdrew consent and one discontinued the drugs). The overall eradication rate was 80.8% (80/99, 95% confidence interval (CI) 72% to 87.4%) in the intention-to-treat (ITT) analysis and was 81.6% (80/98, 95% CI 72.8% to 88.1%) in the per protocol (PP) analysis. The eradication rates in patients who received clarithromycin-based (N=14), levofloxacin-based (N=36), and tetracycline-based (N=49) sequential therapy were 78.6% (11/14), 97.2% (35/36), and 69.4% (34/49) in the ITT analysis, respectively, and were 84.6% (11/13), 97.2% (35/36), and 70.8% (34/48) in the PP analysis, respectively. The eradication rate appeared to be higher in patients treated with clarithromycin and levofloxacin based sequential therapy (92%, 46/50) as compared to those treated with tetracycline-based therapy (69.4%, 34/49) (p=0.007).

Conclusion: This pilot study showed that genotypic resistance guided modified sequential therapy achieved acceptable eradication rate (>80%) in the third line treatment for *H. pylori* infection and was well tolerated. The eradication rate appeared to be higher in patients treated with clarithromycin-based and levofloxacin-based therapy guided by genotypic resistance as compared to those treated empirically with tetracycline-based therapy. Further randomized control trials are needed to directly compare the efficacy of the two strategies. (ClinicalTrials.gov.ID: NCT01032655)

Keywords: *Helicobacter pylori*, sequential therapy, genotypic, resistance, third line, eradication