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Research Project Title：Comparing the Efficacy of Reverse Hybrid Therapy and Concomitant Therapy

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**ABSTRACT**

**Background:** With the rising prevalence of antimicrobial resistance, the failure rate of the standard triple therapy has declined to unacceptable level (<80%) worldwide. A 14-day hybrid therapy invented by our study group appears very promising in *H pylori* eradication, achieving excellent eradication rates of 99% and 97% according to per-protocol and intention-to-treat analyses, respectively. Recently, we reversed the drug administration sequence of hybrid therapy and developed a new two-phase one-step treatment — reverse hybrid therapy. The new therapy is superior to standard triple therapy for *H pylori* eradication, but whether it also achieves a high eradication rate than sequential or concomitant therapy remains unanswered. Additionally, the impacts of reverse hybrid therapy and aforementioned new therapies on gastrointestinal microbiota are unclear.

**Aims:** The aims of this randomized controlled trial are (1) to compare the efficacies of reverse hybrid therapy and concomitant therapy, (2) to investigate the host and bacterial factors predicting the treatment outcomes of the two eradication regimens.

**Methods:** Consecutive 248 *H. pylori*-infected subjects are randomly assigned to receive either a 14-day reverse hybrid therapy or a 14-day concomitant therapy. On recruitment, blood sampling for genotyping of *CYP2C19* is carried out, and antibiotic susceptibility of *H pylori* strains will be checked. Subjects are asked to return at the end of the 2nd week to assess drug compliance and

adverse events. *H pylori* status will be re-assessed at week 6 after the end of anti- *H. pylori* therapy. Finally, the rates of eradication, adverse events and compliance will be compared between groups by chi-square test, and the host and bacterial factors influencing each efficacy of the regimen are assessed by multivariate analysis.

## Introduction

*Helicobacter pylori* (*H. pylori*) infect more than 50% of humans globally. It is the principal cause of chronic gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma (MALToma) [1,2]. In most international guidelines [3-6], standard triple therapy consisting of a proton-pump inhibitor (PPI), clarithromycin and amoxicillin (or metronidazole) for 7 to 14 days is recommended as the choice of treatment for first-line therapy of *H pylori* infection, especially in areas of low clarithromycin resistance (< 15%). Recently, the eradication rates of standard triple therapy have declined to less than 80% in many countries, largely owing to emerging organism resistances [7-10]. Some European studies even reported very poor treatment outcomes of the standard therapy with failure rates of 25-60% [11-13]. Several strategies including sequential therapy, concomitant therapy and hybrid therapy have therefore been proposed to increase the eradication rate [14-16].

Concomitant therapy is another novel regimen proven successful in the presence of clarithromycin resistance [15]. It is a 4-drug regimen containing a PPI (standard dose, b.i.d.), clarithromycin (500 mg, b.i.d.), amoxicillin (1 g, b.i.d.) and metronidazole (500 mg, b.i.d.)

which are all given for the entire duration of therapy. This therapy is superior to standard triple therapy for *H pylori* eradication [17]. It is also less complex than sequential therapy as this regimen does not involve changing drugs halfway through. A head-to-head non-inferiority trial of 10-day sequential and 10-day concomitant therapy showed they were equivalent (93.1% *vs* 93.0% by per-protocol analysis) [18].

Recently, we have developed a new anti-*H pylori* regimen — hybrid therapy , which consists of a dual therapy with a PPI (standard dose, b.i.d.) and amoxicillin (1 g, b.i.d.) for 7 days followed by a quadruple regimen with a PPI (standard dose, b.i.d.), amoxicillin (1 g, b.i.d.), clarithromcyin (500 mg, b.i.d.) and metronidazole (500 mg, b.i.d.) for 7 days [16]. The novel therapy provided excellent eradication rates of 99% and 97% according to per-protocol and intention-to-treat analysis [16]. Several randomized controlled trials subsequently demonstrated that hybrid regimens were comparable with or more effective than sequential regimens [19-22]. It is important to note that the new therapy has a high efficacy in the treatment of *H pylori* strains harboring dual resistance to clarithromycin and metronidazole. Several studies have shown that sequential therapy is ineffective to clear *H pylori* with dual resistance [14]. The prolonging treatment duration of amoxicillin to 14 days in hybrid therapy might account for the higher eradication rate in the face of *H pylori* stains with dual resistance to clarithromycin and metronidazole. A study from Italy [20] which compared markedly different durations of therapy (14-day hybrid therapy *vs* 5-day concomitant therapy) showed that 14-day hybrid therapy was superior by PP analysis (95.7% *vs* 85.1%). However, another

randomized controlled trial showed comparable eradication efficacy between hybrid and concomitant therapies [23]. The study also showed that there was a borderline significant trend toward higher compliance with hybrid therapy compared with concomitant therapy (99% *vs* 95%) [23]. Many expert recommendations therefore proposed hybrid therapy as a treatment option for *H pylori* in areas with moderate or high clarithromycin resistance [24-27].

Switching drugs halfway through the course increases the complexity of an anti-*H pylori* regimen. Reversing the sequence of drug administration (a quadruple regimen followed by a dual regimen) simplifies hybrid therapy and make it become a one-step two-phase therapy. We recently conducted a multi-center, randomized controlled trial to compare the efficacies of reverse hybrid therapy and standard triple therapy [28]. The data indicated that reverse hybrid therapy achieved a higher eradication rate than standard triple therapy (95.5% *vs* 88.6%) by ITT analysis.

Currently, whether reverse hybrid therapy is superior to concomitant therapy in H pylori eradication remains unanswered. Theoretically, the ideal treatment for H pylori infection should be a cheap, highly effective, and well-tolerated therapy. Since the pharmaceutical cost of 14-day reverse hybrid therapy is cheaper than 14-day concomitant therapy, the former would be a better choice than the latter for H pylori eradication if its eradication rate is superior or non-inferior to that of concomitant therapy.We hence conduct the randomized controlled trial are (1) to compare the efficacies of 14-day reverse hybrid therapy and 14-day concomitant therapy, (2) to investigate the host and bacterial factors predicting the treatment outcomes of the two eradication regimens.

## PATIENTS & METHODS

### Study population

The open-labeled trial is conducted at the Kaohsiung Veterans General Hospital and Kaohsiung Medical University Hospital in Taiwan in accordance with the principles of good clinical practice from the Declaration of Helsinki. The study protocol will be approved by the Ethics Committees of the Kaohsiung Veterans General Hospital and the Kaohsiung Medical University Hospital. All patients give written informed consent before participating in the study.

We will recruit 248 patients to the study if they meet the following criteria: they are adult patients aged ≥ 20 years and have *H pylori* infection. The exclusion criteria include The exclusion criteria include (1) previous *H pylori*-eradication therapy, (2) patient with allergic history to the medications used, (3) patients with previous gastric surgery, (4) coexistence of serious concomitant illness (for example, decompensated liver cirrhosis, uremia), and (5) pregnant women.

### *Randomization and treatment*

This is a randomized controlled trial. Eligible *H. pylori*-infected subjects are randomly assigned to a 14-day reverse hybrid therapy (a 7-day quadruple regimen with dexlansoprazole MR 60 mg once daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily, and metronidazole 500 mg twice daily, followed by a 7-day dual regimen with dexlansoprazole MR 60 mg once daily and amoxicillin 1 g twice daily) or a 14-day concomitant therapy (dexlansoprazole

MR 60 mg once daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily, and metronidazole 500 mg twice daily for 14 days). All drugs are taken one hour before breakfast or dinner. Patients with peptic ulcers in initial endoscopy receive an additional 4-week dexlansoprazole MR therapy (60 mg orally once daily), while patients with symptomatic gastritis only take additional four-weeks of antacid.

On recruitment, patients are requested to complete a standard record for a complete medical history and demographic data. Additionally, blood sampling for genotyping of *CYP2C19* is carried out. To assess eradication efficacy and status of ulcer healing, repeated endoscopy with rapid urease test, histological examination and culture is performed for peptic ulcer patients at the sixth week after the end of anti- *H. pylori* therapy. Urea breath test is conducted to assess *H. pylori* status in the subjects with gastritis and in peptic ulcer subjects who refuse follow-up endoscopy,. Eradication is defined as (1) negative results of both rapid urease test and histology, or (2) a negative result of urea breath test.

Finally, the eradication rates by both intention-to-treat and per-protocol analyses, adverse events and compliance will be compared between groups by chi-square test, and the host and bacterial factors influencing the efficacy of eradication therapy are assessed by multivariate analysis.

***Statistical analysis***

The primary outcome variable is eradication rate. The secondary outcome variables are the rate

of adverse events and compliance. Chi-square test with or without Yates correction for continuity and Fisher's exact test are used when appropriate to compare the major outcomes between groups using the SPSS program (version 10.1, Chicago, Illinois, USA). A *P* value less than 0.05 is considered statistically significant.

Eradication rates are evaluated by ITT and per-protocol (PP) analyses. ITT analysis includes all randomized patients who have taken at least one dose of study medication. Patients whose infection status is unknown following treatment are considered treatment failures for the purposes of ITT analysis. The PP analysis excludes the patients with unknown *H. pylori* status following therapy and those with major protocol violations.

To determine the independent factors affecting the treatment response, Host and bacterial parameters are analyzed by univariate analysis. These variables include the following: age (<60 or ≥60 years), gender, history of smoking, history of alcohol consumption (<80 g/day or ≥80 g/day), ingestion of coffee (<1 cup/day or ≥1 cup/day), ingestion of tea ((<1 cup/day or ≥1 cup/day), coexistence of a systemic disease (yes or no), previous history of peptic ulcer disease, endoscopic appearance (ulcer or gastritis), CYP2C19 polymorphism, drug compliance (good or poor), and antibiotic susceptibility. Those variables found to be significant by univariate analysis are subsequently assessed by a stepwise logistic regression method to identify independent factors for eradication outcome.

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