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Research Project Title ： Comparing the efficacy and impact on gastrointestinal microbiome of reverse hybrid therapy and bismuth quadruple therapy in *Helicobacter pylori* eradication
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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 demonstrated that the eradication rate of reverse hybrid therapy was higher than that of standard triple therapy. However, whether reverse hybrid therapy achieves a higher eradication rate than bismuth quadruple therapy remained unanswered.

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

Methods: Consecutive 352 *H. pylori*-infected subjects are randomly assigned to receive either a 14-day reverse hybrid therapy or a 14-day bismuth quadruple 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*) infection is the principal cause of chronic gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma.[1] In most international guidelines,[2-4] 14-day standard triple therapy is still recommended as a choice of treatment for the first-line therapy of *H. pylori* infection, especially in areas of low

clarithromycin resistance (≤ 15%). However, the eradication rates of standard triple therapy have declined to less than 80% in most countries because of the rising prevalence of clarithromycin resistance.[5] Several strategies including bismuth-containing quadruple therapy and non-bismuth-containing quadruple therapy have therefore been proposed to increase the eradication rate.[5,6]

In the Maastricht V/Florence Consensus Report,[3] bismuth quadruple therapy is the treatment of choice for the first-line therapy of *H. pylori* infection in areas of high clarithromycin resistance (> 15%) and an alternative in areas of low clarithromycin resistance. In the recent American College of Gastroenterology (ACG) guideline, it is also recommended as a first-line treatment for *H. pylori* infection.[4] However, the complicated administration of bismuth quadruple therapy easily reduces the adherence of patients, and the complex therapy is associated with a high frequency of adverse events.[7,8]

Hybrid therapy developed by Hsu et al. in 2011 consists of a dual therapy with a proton pump inhibitor (PPI) and amoxicillin for 7 days followed by a quadruple regimen with a PPI, amoxicillin, clarithromycin and metronidazole for 7 days.[6] It achieved an eradication rate of 97.4% by intention-to-treat (ITT) analysis and 99.1% by per-protocol (PP) analysis in Taiwan.[6] Subsequent randomized controlled trials demonstrated that 14-day hybrid therapies were comparable or more effective than 10-day sequential therapies.[9,10] A recent large multicentre randomized controlled trial documented that 14-day hybrid and 14-day concomitant therapies had comparable efficacy in the treatment of *H. pylori* infection, and both could cure more than 90% of patients with *H. pylori* infections in areas of high clarithromycin and metronidazole resistance.[11] Currently, it is a recommended first-line

treatment choice in the ACG guideline[4] and the Taiwan *Helicobacter pylori* Consensus Report.[12]

However, hybrid therapy requires additional two antibiotics in the last 7 days, which can confuse patients and may dampen enthusiasm for its use. Reversing the sequence of drug administration (a quadruple regimen followed by a dual regimen) can simplify hybrid therapy. The aims of this randomized controlled trial are (1) to compare the efficacies of reverse hybrid therapy and bismuth quadruple 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 352 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 pantoprazole 40 mg twice 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 pantoprazole 40 mg twice daily and amoxicillin 1 g twice daily) or a 14-day bismuth quadruple therapy (pantoprazole 40 mg twice daily, bismuth tripotassium dicitrate 120 mg, and tetracycline 500 mg four times daily for 14 days). All drugs are taken one hour before breakfast and dinner. Patients with peptic ulcers in initial endoscopy receive an additional 4-week pantoprazole therapy (40 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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