Reverse hybrid therapy achieves a similar eradication rate as standard hybrid therapy for *Helicobacter pylori* infection

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Abstract

Background: Reverse hybrid therapy is a simplified hybrid treatment for *Helicobacter pylori* infection. It achieves a higher eradication rate than standard triple therapy. This study aimed to compare the efficacies of reverse hybrid and hybrid therapies in the treatment of *H. pylori* infection.

Methods: From September 2008 to September 2017, 490 *H. pylori*-infected patients who received 14 days of reverse hybrid therapy (proton pump inhibitor plus amoxicillin for 14 days and clarithromycin plus metronidazole for the initial 7 days; n = 252) or hybrid therapy (proton pump inhibitor plus amoxicillin for 14 days and clarithromycin plus metronidazole for the final 7 days; n = 238) were included in this retrospective cohort study. *Helicobacter pylori* status was examined 6–8 weeks after therapy.

Results: The eradication rates of the reverse hybrid and hybrid therapies by modified intention-to-treat analysis were comparable (96.4% vs 96.6%; $p = 0.899$). There were no differences in the efficacy of eradication between therapies for clarithromycin-resistant strains (87.0% vs 90.0%) or metronidazole-resistant strains (97.7% vs 100.0%). In addition, there were comparable frequencies of adverse events for both treatments (18.7% vs 13.0%) and treatment adherence (94.4% vs 97.1%).

Conclusion: Reverse hybrid therapy can achieve a similar eradication rate to hybrid therapy for *H. pylori* infection.

Keywords: *Helicobacter pylori*; Hybrid therapy; Reverse hybrid therapy

1. INTRODUCTION

Helicobacter pylori infection is the major cause of chronic gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.[1,2] With the rising prevalence of clarithromycin-resistant strains, standard triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin (or metronidazole) for *H. pylori* infection has declined to <80% in most countries.[3–5] Therefore, several alternative therapies, such as bismuth-containing quadruple therapy or non-bismuth quadruple therapy (e.g., sequential, concomitant or hybrid therapy), were developed to increase the eradication efficacy in areas with high clarithromycin resistance.[6,7]

Hybrid therapy first reported by Hsu et al. consists of a dual therapy with a PPI and amoxicillin for 7 days followed by a quadruple regimen with a PPI, amoxicillin, clarithromycin, and metronidazole for 7 days.[8] It exhibited an excellent eradication rate with 99% by per-protocol (PP) analysis and 97% by intention-to-treat (ITT) analysis in the pilot trial.[8] Subsequent randomized controlled studies further demonstrated that hybrid therapy was comparable with or more effective than sequential therapy.[9–11] Additionally, a recent multicenter randomized controlled trial showed that both 14-day hybrid and 14-day concomitant therapies cured >90% of patients with *H. pylori* infections in regions of high clarithromycin and metronidazole resistance.[12] Currently, hybrid therapy is a recommended first-line treatment for *H. pylori* infection in the American College of Gastroenterology guideline,[13] Bangkok Consensus Report,[14] and Taiwan *H. pylori* Consensus Report.[15]

Nonetheless, 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

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regimen) can simplify hybrid therapy (Figure 1). It is not necessary for patients to remember to take two additional antibiotics in the last 7 days during anti-*H. pylori* treatment. A recent randomized controlled study showed that reverse hybrid therapy achieved a higher eradication rate than standard triple therapy.[16] Additionally, it is not inferior to bismuth quadruple therapy in the first-line treatment of *H. pylori* infection and has fewer side effects.[17]

Currently, whether changing the drug administration sequence of hybrid regimen would influence the eradication efficacy of hybrid therapy remains unclear. To clarify this issue, we conducted the retrospective study to compare the efficacies of reverse hybrid therapy and standard hybrid therapy in the first-line treatment of *H. pylori* infection.

2. METHODS

2.1 Study Participants

From September 2008 to September 2017, consecutive *H. pylori*-infected patients undergoing a 14-day reverse hybrid therapy or a hybrid therapy who received a complete follow-up were included for the retrospective cohort study. The diagnosis of *H. pylori* infection was based on at least two positive results of rapid urease test, histology and culture or a positive result of urea breath test. Exclusion criteria were as follows: (1) previous eradication treatment; (2) consumption of antibiotics within the prior 4 weeks; (3) allergy to clarithromycin, amoxicillin, or metronidazole; (4) patients with previous gastric surgery; (5) existence of severe concomitant illness; and (6) pregnancy or lactation. The study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS18-CT5-06).

2.2 Study design

In total, 252 patients receiving a reverse hybrid therapy (a PPI plus amoxicillin 1 g twice daily for 14 days, and clarithromycin 500 mg plus metronidazole 500 mg twice daily for the final 7 days), and 238 patients receiving a hybrid therapy (a PPI plus amoxicillin 1 g twice daily for 14 days, and clarithromycin 500 mg plus metronidazole 500 mg twice daily for the final 7 days) were included for the study. All patients were prospectively followed up with a standard protocol by well-trained research assistants. The medications were taken 1 hour before breakfast and dinner.

A complete medical history and demographic data were obtained from each patient with a standard checklist. Patients were asked to return at the end of week 2 to assess adverse events and drug adherence. A four-point scale system was used, including none, mild (discomfort annoying but not interfering with daily life), moderate (discomfort sufficient to interfere with daily life), and severe (discomfort resulting in discontinuation of eradication therapy).[18] Poor drug adherence was defined as taking <80% of pills.

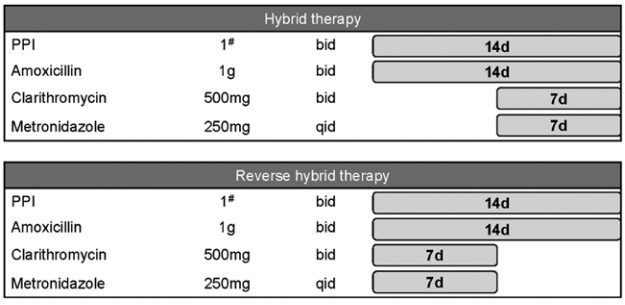

Fig. 1. Regimens of reverse hybrid therapy and hybrid therapy.

A urea breath test or a follow-up endoscopy with rapid urease test and histological examination was performed at 6 to 8 weeks after the end of anti-*H. pylori* therapy. Eradication was defined as: (1) a negative result of the urea breath test; or (2) negative results of both rapid urease test and histology.[18,19] The antibiotic susceptibility of *H. pylori* strains were evaluated by E-test (AB Biodisk, Solna, Sweden). *Helicobacter pylori* strains with a minimal inhibitory concentration value >1 μg/mL, >0.5 μg/mL, and >8 μg/mL were considered to be resistant to clarithromycin, amoxicillin, and metronidazole, respectively.[20,21]

2.3 Statistical analysis

This retrospective study only included patients who had received follow-up *H. pylori* tests. The primary outcome was cure of *H. pylori* infection. Eradication rate was assessed by modified ITT analysis and PP analysis. Modified ITT analysis included all patients who received at least one dose of eradication drugs regardless their drug adherence. The PP analysis excluded the patients with poor drug adherence. The secondary outcomes were the frequencies of adverse events and treatment adherence. The differences in demographic data, eradication rates, adverse events, and drug adherence were determined appropriately by Chi-square test or Fisher exact test. The continuous data were compared by Student t test. SPSS (version 20 for Microsoft Windows) was used for statistical analyses. A p-value <0.05 was considered statistically significant. To search the independent factors affecting eradication rate of hybrid regimens, clinical, endoscopic, and antibiotic susceptibility parameters were analyzed by univariate analysis. Significant parameters in univariate analysis were further analyzed by a logistic regression method to identify the independent factors predicting eradication failure. Clinical and endoscopic variables included age (< 60 or ≧ 60 years); sex; history of current smoking (< 1 pack/week or ≧ 1 pack/week), alcohol use (< 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), endoscopic appearance (ulcer or gastritis), type of PPI; and drug adherence (good or poor).

3. RESULTS

A total of 252 *H. pylori*-infected patients received a 14-day reverse hybrid therapy (pantoprazole-based treatment, n = 192; dexlansoprazole-based treatment, n = 60), and 238 patients received a 14-day hybrid therapy (pantoprazole-based treatment, n = 165; esomeprazole-based treatment, n = 73). The baseline characteristics of the patients are shown in Table 1. The two patient groups had comparable age, gender, smoking, alcohol consumption, underlying diseases, endoscopic findings, and antibiotic resistance. In this study, 21 patients with poor drug adherence (reverse hybrid therapy, n = 14; hybrid therapy, n = 7) were excluded from PP analysis.

3.1 Eradication of *H. pylori*

Table 2 displays the clinical outcomes of the two eradication therapies in the treatment of *H. pylori* infection. Reverse hybrid and hybrid therapies had comparable eradication rate by modified ITT analysis (96.4% vs 96.6%; p = 0.899). Per-protocol analysis showed similar results (96.6% vs 96.5%; p = 1.000). Table 3 displays the impacts of antibiotic resistances on the eradication rates of reverse hybrid and hybrid therapies. In the reverse hybrid therapy group, the eradication rates of *H. pylori* strains with nonresistance, single clarithromycin resistance, single metronidazole resistance, and dual resistances were 98.8%,

Table 1

Demographic data and antibiotic resistance of 14-day hybrid and 14-day reverse hybrid therapies

Characteristics	Hybrid therapy (n = 238)	Reverse hybrid therapy (n = 252)	*p*
Age (year) (mean ± SD)	54.2 ± 12.1	54.8 ± 12.8	0.954
Gender (males/females)	126/112	123/129	0.361
Smoking	56 (23.5%)	45 (17.9%)	0.121
Alcohol consumption	14 (5.9%)	16 (6.3%)	0.829
Underlying diseases	66 (27.7%)	78 (31.0%)	0.434
Endoscopic findings			0.081
Gastritis	85 (35.7%)	119 (47.2%)	
Gastric ulcer	69 (29.0%)	62 (24.6%)	
Duodenal ulcer	42 (17.6%)	35 (13.9%)	
Gastric ulcer and duodenal ulcer	42 (17.6%)	36 (14.3%)	
Antibiotic resistance			
Clarithromycin	10/88 (11.4%)	23/140 (16.4%)	0.290
Metronidazole	31/88 (35.2%)	44/140 (31.4%)	0.552
Amoxicillin	1/88 (1.1%)	0/140 (0%)	0.386

Table 2

The major outcomes of 14-day hybrid and 14-day reverse hybrid therapies

	Eradication rate		
	Hybrid therapy (n = 238)	Reverse hybrid therapy (n = 252)	*p*
Eradication rate Intention-to-treat	96.6% (280/238)	96.4% (243/252)	0.899
Per-protocol	96.5% (223/231)	96.6% (230/238)	1.000
Adverse events	13.0% (31/238)	18.7% (47/252)	0.089
Compliance	97.1% (231/238)	94.4% (238/252)	0.153

Table 3

Impact of antibiotic resistance on the eradication rate of hybrid and reverse hybrid therapy

Susceptibility pattern	Hybrid therapy (n = 88)	Reverse hybrid therapy (n = 140)	*p*
Cla^S—Met^S	52/52 (100%)	80/81 (98.8%)	1.000
Cla^S—Met^R	26/26 (100%)	36/36 (100%)	—
Cla^R—Met^S	4/5 (80.0%)	13/15 (86.7%)	1.000
Cla^R—Met^R	5/5 (100%)	7/8 (87.5%)	1.000

^{S} = sensitive strains; ^{R} = resistant strains

86.7%, 100%, and 87.5%, respectively. In the hybrid therapy group, the corresponding eradication rates were 100%, 80%, 100%, and 100%, respectively. There were no significant differences in the eradication rates between the two therapies for eradicating *H. pylori*-resistant strains.

3.2 Adverse events and drug adherence

The frequencies of adverse events in the participants receiving reverse hybrid and hybrid therapies were 18.7% and 13.0%, respectively. The two treatments exhibited comparable frequencies of adverse events (p = 0.089). Table 4 demonstrates all the side effects of the two therapies. The reverse hybrid group had a higher frequency of abdominal pain than hybrid group (4.4% vs 0.4%, respectively, p = 0.006). However, there were no significant differences with respect to other adverse effects. In the reverse hybrid group, 13 patients stopped anti-*H. pylori* treatment due to abdominal pain (n = 1), taste perversion (n = 1), nausea (n = 3), vomiting (n = 1), skin rash (n = 3), fatigue (n = 1), and others (n = 3). On the other hand, in the hybrid group, 10 patients stopped anti-*H. pylori* treatment due to diarrhea (n = 3), dizziness (n = 1), nausea (n = 3), skin rash (n = 1), and others (n = 2).

Table 4

Adverse events of 14-day hybrid and 14-day reverse hybrid therapies

Adverse Events	Hybrid therapy (n = 238)	Reverse hybrid therapy (n=252)	*p*
Abdominal pain	1 (1/0/0)	11 (7/3/1)†	0.006*
Constipation	1 (1/0/0)	0 (0/0/0)	0.486
Diarrhea	3 (0/0/3)	9 (5/4/0)	0.143
Dizziness	9 (7/1/1)	5 (3/2/0)	0.233
Taste perversion	4 (2/2/0)	11 (7/3/1)	0.115
Headache	5 (3/2/0)	2 (1/1/0)	0.273
Anorexia	0 (0/0/0)	0 (0/0/0)	—
Nausea	13 (7/3/3)	20 (7/10/3)	0.275
Vomiting	2 (2/0/0)	5 (1/3/1)	0.286
Skin rash	5 (3/1/1)	6 (2/1/3)	0.834
Fatigue	3 (1/2/0)	5 (3/1/1)	0.725
Others	3 (1/0/2)	7 (3/1/3)	0.341

* $p < 0.05$.

† No. patients who suffered from mild, moderate, and severe adverse events.

In this study, 14 patients in the reverse hybrid group and 7 patients in the hybrid group did not complied with the eradication treatment. The two therapies exhibited comparable drug adherence (94.4% vs 97.1%; p = 0.153).

3.3 Factors influencing efficacy of anti-*H. pylori* therapy

Table 5 lists the factors affecting eradication rates of anti-*H. pylori* therapies in all the patients included in this study. There was a significant difference in eradication rate between clarithromycin-resistant and clarithromycin-susceptible stains (87.9% and 99.5%; p = 0.002). The other factors including smoking, presence of peptic ulcer, drug adherence, and metronidazole resistance did not significantly affect eradication efficacy. Multiple regression analysis demonstrated that clarithromycin resistance was the only independent factor predicting eradication failure with an odds ratio of 25.8 (95% CI, 2.9–247.3; p = 0.004).

4. DISCUSSION

This is the first study to compare the efficacies of 14-day reverse hybrid and 14-day hybrid therapies for the first-line treatment of *H. pylori* infection. Our results demonstrated several novel findings. First, the two therapies had an equivalent efficacy (96.6% vs 96.4%) for the treatment of *H. pylori* infection. Second, the two treatments exhibited comparable overall frequencies of adverse events (18.7% vs 13.0%) and drug adherence (94.4% vs 97.1%). Third, both therapies could achieve a high eradication rate for both clarithromycin-resistant strains (87.0% vs 90.0%) and metronidazole-resistant strains (97.7% vs 100.0%). These findings clearly indicate that the sequence of antibiotic administration in the hybrid regimen did not influence the efficacy of anti-*H. pylori* therapy. This important finding is consistent with our previous study that showed equivalent efficacies of 10-day reverse sequential and 10-day sequential therapies in the treatment of *H. pylori* infection.[22]

Table 5

Univariate analysis of the clinical factors influencing the efficacy of *H. pylori* eradication therapy.

Principle parameter	No. patients	Eradication rate	*p*
Age			0.726
<60 year	308	96.8%	
≧60 year	182	96.2%	
Sex			0.193
Females	241	95.4%	
Males	249	97.6%	
Smoking			0.544
(−)	389	96.1%	
(+)	101	98.0%	
Alcohol consumption			1.000
(−)	460	96.5%	
(+)	30	96.7%	
Ingestion of coffee			1.000
(−)	361	96.4%	
(+)	129	96.9%	
Ingestion of tea			0.418
(−)	351	96.0%	
(+)	139	97.8%	
NSAID use			0.248
(−)	482	96.7%	
(+)	8	87.5%	
Presence of ulcer			0.644
(−)	204	96.1%	
(+)	286	96.9%	
Eradication regimen			1.000
Hybrid	238	96.6%	
Reverse hybrid	252	96.4%	
Compliance			0.531
Good	469	96.6%	
Poor	21	95.2%	
Type of PPI			0.179
Pantoprazole	357	95.8%	
Esomeprazole	73	100.0%	
Dexilansoprazole	60	96.7%	
Clarithromycin			0.002*
Susceptible	195	99.5%	
Resistant	33	87.9%	
Metronidazole			1.000
Susceptible	153	97.4%	
Resistant	75	98.7%	
Amoxicillin			1.000
Susceptible	227	97.8%	
Resistant	1	100%	

*$p < 0.05$

PPI = proton pump inhibitor.

The strengths of this study include the large sample size (n = 490) and the large amount of data assessing the impact of antibiotic resistance on the eradication rates of hybrid regimens. Determining the antibiotic resistance of 228 strains allowed us to predict the performance of the two therapies in regions with different prevalence rates of clarithromycin and metronidazole resistance. In the current study, the eradication rates of *H. pylori* strains with no resistance, resistance to clarithromycin alone, resistance to metronidazole alone, and dual resistance in the patients receiving reverse hybrid therapy were 98.8%, 86.7%, 100%, and 87.5%, respectively, compared with 100%, 80%, 100%, and 100% for those receiving hybrid therapy. These results indicated that both 14-day reverse hybrid therapy and 14-day hybrid therapy can be recommended in areas with either high or low clarithromycin and metronidazole resistance. A recent multicenter randomized controlled trial conducted in Spain and Italy confirmed that 14-day hybrid therapy could cure >90% of patients with *H. pylori* infection in areas with high clarithromycin and metronidazole resistance.[12]

In this study, the patients who received reverse hybrid therapy had a higher frequency of abdominal pain than those who received hybrid therapy (4.4% vs 0.4%), although the overall frequencies of adverse events with the two therapies were comparable. The reason for this difference in the frequency of abdominal pain is unknown; however, several studies have shown that anti-*H. pylori* therapy can lead to dysbiosis of gut microbiota,[23,24] and that probiotic supplementation can reduce anti-*H. pylori* eradication therapy-related dysbiosis, thereby decreasing the frequency of adverse effects.[23,25,26] A recent microbiota study also demonstrated that the relative abundance of phylum Proteobacteria in patients with adverse effects was higher than that in patients without adverse effects during anti-*H. pylori* treatment.[27] We therefore hypothesize that reverse hybrid therapy using three antibiotics in the initial phase of treatment may lead to more severe dysbiosis of the gut microbiota and more side effects than hybrid therapy, which uses only one antibiotic in the initial phase of treatment. Further studies are warranted to investigate the mechanisms underlying the association between dysbiosis induced by anti-*H. pylori* therapy and the development of adverse effects.

Clarithromycin resistance has been reported to be the main reason for the failure of standard triple therapy.[28–30] Large-scale randomized controlled trials have also demonstrated that clarithromycin resistance can decrease the efficacy of sequential therapy.[30,31] Although several previous randomized studies did not show a significant impact of clarithromycin resistance on the eradication efficacy of hybrid or reverse hybrid therapies,[17,32] patients with clarithromycin-resistant strains receiving hybrid or reverse hybrid therapies had a lower eradication rate than those with clarithromycin-susceptible strains (87.9% vs 99.5%) in this study. In addition, multivariate analysis revealed that clarithromycin resistance was an independent predictor of eradication failure with the hybrid regimens. Possible explanations for the discrepancies in the impact of clarithromycin resistance on the eradication rate of hybrid regimens include different study powers, variable metronidazole resistance rates, and different frequencies of *CYP2C19* genotypes.

In eradication therapy, PPIs not only increase the activity of antibiotics by reducing gastric acid secretion but also have direct anti-*H. pylori* activity.[33] Most PPIs are metabolized by the hepatic cytochrome P450 system, and particularly *CYP2C19*. Several studies have reported that the *CYP2C19* genotype or the type of PPI was a factor affecting the eradication efficacy of anti-*H. pylori* therapies.[34,35] In the current study, the eradication rates of pantoprazole-, esomeprazole-, and dexilansoprazole-based hybrid treatments were all >95%, and no significant differences in eradication rates were observed between the patients receiving different PPI-based eradication therapies. These findings suggest that the type of PPI does not influence the efficacy of hybrid regimens.

There are several limitations to this study. First, it was not a randomized controlled trial, so the findings in this retrospective cohort study could be due to channeling bias. Nonetheless, all consecutive patients in the study were prospectively followed up according to a standard protocol, and adverse events and drug adherence were recorded by trained assistants via a standardized questionnaire. Second, *H. pylori* cultures were not routinely performed, which may raise the possibility of selection bias. Nonetheless, we used multivariate analysis to identify the independent factors for eradication outcomes.

In conclusion, 14-day reverse hybrid therapy and hybrid therapy had comparable eradication rates in the first-line treatment of *H. pylori* infection in this study. Both treatments achieved

a high eradication rate for both clarithromycin-resistant and metronidazole-resistant strains.

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