Hybrid, sequential and concomitant therapies for Helicobacter pylori eradication: A systematic review and meta-analysis

Zhi-Qiang Song, Li-Ya Zhou

Zhi-Qiang Song, Li-Ya Zhou, Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China

Author contributions: Song ZQ contributed to article retrieval, data extraction, analysis and interpretation of data, statistical analyses, and manuscript preparation; Zhou LY contributed to study conception and design, analysis and interpretation of data, manuscript revision; both authors have read and approved the final manuscript.

Supported by National Science and Technology Pillar Program of 12th Five-Year Plan in China, No. 2012BAI06B02; Clinical Key Projects of Peking University Third Hospital, No. Y76493-03; Key Laboratory for Helicobacter pylori Infection and Upper Gastrointestinal Diseases in Beijing, No. BZ0371.

Conflict-of-interest statement: The authors deny any conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Li-Ya Zhou, BS, Department of Gastroenterology, Peking University Third Hospital, No 49, North Garden Road, Haidian District, Beijing 100191, China. liyazhou3352@sina.com Telephone: +86-18910192576 Fax: +86-10-82265021

Accepted: January 30, 2016 Article in press: January 30, 2016 Published online: May 21, 2016

Abstract

AIM: To compare hybrid therapy (HT) with traditional sequential therapy (ST) and concomitant therapy (CT) for Helicobacter pylori (H. pylori) eradication.

METHODS: We performed an electronic search of PubMed, Embase, and the CENTRAL database. Randomized controlled trials (RCTs) of HT were included in the meta-analysis. The primary outcome was the eradication rate of H. pylori. The secondary outcomes included the compliance rate and adverse event rate. Effect estimates were pooled using the random-effects model.

RESULTS: Twelve studies were included. Pooled results showed no significant differences in eradication rate between HT and ST in per-protocol (PP) analysis (RR = 1.03, 95%CI: 0.94-1.12, P = 0.59) or in intention-to-treat (ITT) analysis (RR = 1.00, 95%CI: 0.89-1.12, P = 0.94). HT and ST showed similarly high compliance rate (96% vs 98%, P = 0.55) and acceptable adverse event rate (30.3% vs 28.2%, P = 0.63). No significant results were seen in the eradication rate between HT and CT in PP analysis (RR = 1.01, 95%CI: 0.96-1.05, P = 0.76) or in ITT analysis (RR = 0.99, 95%CI: 0.95-1.03, P = 0.47). HT displayed a slightly higher compliance rate than CT (95.8% vs 93.2%, P < 0.05). The adverse event rates of HT and CT were similar (39.5% vs 44.2%, P = 0.24).

CONCLUSION: Compared with ST or CT, HT yields a similar eradication rate, high compliance rate, and acceptable safety profiles.
INTRODUCTION

Approximately 50% of the global population are infected with *Helicobacter pylori* (*H. pylori*). The presence of *H. pylori* in the stomach is directly associated with a series of gastric diseases, including chronic gastritis, peptic ulcer, and gastric cancer[1]. Triple therapy, consisting of one proton pump inhibitor (PPI), amoxicillin, and clarithromycin, has been established as the standard first-line treatment for *H. pylori* eradication since the 1997 Maastricht Conference[2]. However, the eradication rates have decreased to unacceptable levels (less than 80%) in many countries[3]. Growing resistance of *H. pylori* strains to clarithromycin and metronidazole is the major cause of treatment failure[4,5].

Worldwide efforts led to the development of new regimens to improve the eradication rate. Sequential therapy is one of the latest innovations, which was introduced by Zullo et al[6] in 2003. It entails the use of a PPI and amoxicillin for the first 5-7 d, followed by 5-7 d of PPI-clarithromycin-metronidazole (or tinidazole)[2,3]. With less clarithromycin resistance[3], the sequential regimen was more effective than standard triple therapy for *H. pylori* eradication[7,8]. However, some researchers argued that the benefit of sequential therapy only resulted from additional antibiotic therapy. Thus, it has been postulated that the four components of sequential therapy could be administered concurrently as concomitant therapy comprising PPI-clarithromycin-amoxicillin-metronidazole over several days[9]. The latest guideline recommends sequential and concomitant therapies as alternative first-line treatment in areas with a high rate of clarithromycin resistance[2].

Hybrid therapy entails administration of amoxicillin and a PPI for 5-7 d, followed by a PPI, amoxicillin, metronidazole, and clarithromycin for 5-7 d[10]. The recent randomized clinical trials (RCTs) of hybrid therapy showed conflicting results. Two studies showed that hybrid therapy outperformed sequential therapy in *H. pylori* eradication[11]. However, similar eradication rates were presented by other studies[12-14]. Furthermore, the duration of sequential or concomitant therapy was inconsistent between the studies. Therefore, we conducted this meta-analysis to evaluate the efficacy of hybrid therapy. We compared the efficacy, compliance, and safety of this new therapy with sequential or concomitant therapy.

MATERIALS AND METHODS

Search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement[15]. Two reviewers independently performed systematic literature search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception through October 2015. The search strategy is shown in Table 1. We used the following keywords or MESH Terms: "helicobacter pylori" or "H. pylori", "hybrid" or "sequential-concomitant". The language was limited to English. We also manually searched the references of eligible studies in case of any omission.

Inclusion criteria

Studies meeting the following inclusion criteria were included in the meta-analysis: (1) comparison of hybrid therapy (proton-pump inhibitors and amoxicillin for 5 to 7 d, followed by proton-pump inhibitors, amoxicillin, clarithromycin, and metronidazole for another 5 to 7 d) with other treatment regimens (sequential therapy, concomitant therapy, or triple therapy) in patients with *H. pylori* infection, or comparing different durations of hybrid therapy; (2) randomized controlled trials (RCTs); (3) *H. pylori* infection was diagnosed with rapid urease test, 13C-urea breath test, histology, or culture; and (4) comparison of the eradication rate, compliance, and/or adverse events. The *H. pylori* eradication was assessed by UBT at least 4 wk after treatment.

Data extraction and quality assessment

Two authors independently abstracted the data using a standardized form. The following data were collected from each study: author and year, study design, country, sample size, gender, comparison arms, diagnosis of *H. pylori*, eradication of *H. pylori*, and follow-up. The quality of the included study was evaluated by the Jadad scale, which assessed the study quality by randomization (2 points), blinding (2...
Statistical analysis

The effect size was calculated as the relative risk (RR) and the 95% confidential interval (CI) for each dichotomous outcome. The meta-analysis was conducted using the STATA software (StataCorp LP, College Station, TX, United States). The eradication rate, compliance rate and side effects rate were pooled by the Comprehensive Meta-Analysis statistical package (CMA Version 2.2, Biostat, Englewood, NJ, United States). The random-effects model using the DerSimonian and Laird method was employed for pooling the data because of suspected heterogeneity. The heterogeneity was evaluated by the Cochran’s Q statistic (statistical significance defined as $P < 0.05$), and the $I^2$ statistic (significant heterogeneity defined as $I^2 > 50\%$). Intention-to-treat (ITT) analysis was preferred to a per-protocol (PP) approach. The non-

### Table 1 Characteristics of included studies involving hybrid therapy

| Ref.          | Region       | Design       | No. of patients | Age, mean or range, yr | Men, % | Hybrid group                                                                                           | Control group  | Confirmation of infection | Confirmation of eradication | Follow-up | Jadad score |
|---------------|--------------|--------------|-----------------|------------------------|--------|--------------------------------------------------------------------------------------------------------|-----------------|--------------------------|--------------------------------|------------|-------------|
| Hsu et al[10](2011) | Taiwan       | Single-arm   | 117             | 54                     | 50     | E 40 mg + A 1g, bid, 7d; E 40 mg + A 1g + C 500 mg + M 500 mg, bid, 7d | NA              | RUT, UBT, and histology                                      | UBT 8w                                        | NA          |             |
| Sardarian et al[28](2012) | Iran         | RCT          | 420             | 43                     | 48     | P 40 mg + A 1g, bid, 7d; P 40 mg + A 1g + C 500mg + T 500mg, bid, 7d | Sequential therapy (P 40 mg + A 1g, bid, 5d; P 40 mg + C 500mg + T 500mg, bid, 5d) | RUT and/or histology                                      | UBT 8w                                        | 3            |             |
| Molina-Infante et al[27](2013) | Spain, Italy | RCT          | 343             | 18-87                  | 49     | O 40 mg + A 1g bid, 7d; O 20 mg + A 1g + C 500 mg + N 500 mg, bid, 7d | Concomitant therapy (O 20 mg + A 1g + C 500 mg + N 500 mg, bid, 14d) | UBT or any two of RUT, histology, or culture                     | UBT 8w                                        | 3            |             |
| Zullo et al[11](2013) | Italy        | RCT          | 270             | 49                     | 41     | O 40 mg + A 1g bid, 7d; O 20 mg + A 1g + C 500 mg + T 500 mg, bid, 7d | Concomitant therapy (O 20 mg + A 1g + C 500 mg + T 500 mg, bid, 5d); sequential therapy (O 20 mg + A 1g, bid, 5d; O 20 mg + C 500mg + T 500 mg, bid, 5d) | RUT and histology                                      | UBT 6w                                        | 3            |             |
| Oh et al[25](2014) | Korea        | RCT          | 184             | 57                     | 37     | R 20 mg + A 1g, bid, 7d; R 20 mg + A 1g + C 500 mg + M 500 mg, bid, 7d | Sequential therapy (R 20 mg + A 1g, bid, 7d; R 20 mg + M 500 mg, bid, M 500 mg, qd, 7d) | RUT or histology                                      | UBT 6w                                        | 3            |             |
| De Francesco et al[24](2014) | Italy        | RCT          | 440             | 47                     | 42     | O 20 mg + A 1g bid, 7d; O 20 mg + A 1g + C 500 mg + M 500 mg, bid, 7d | Concomitant therapy (O 20 mg + A 1g + C 500 mg + M 500 mg, bid, 5d or 14d); sequential therapy (R 20 mg + A 1g, bid, 7d; R 20 mg + M 500 mg, bid, Mo 500 mg, qd, 7d or 14d) | RUT+histology                                      | UBT 6-8w                                      | 2            |             |
| Wu et al[23](2014) | Taiwan       | RCT          | 220             | 53                     | 49     | E 20 mg + A 1g bid, 5d; E 20 mg + A 1g + C 500 mg + M 500 mg, bid, 7d | Hybrid therapy (E 20 mg + A 1g bid, 5d/7d; E 20 mg + A 1g + C 500 mg + M 500 mg, bid, 7d) | RUT, UBT, histology, or culture                          | UBT or triple negative (RUT + histology + culture)            | 8w            | 3            |             |
| Cuadrado-Lavin et al[28](2015) | Spain        | RCT          | 300             | 44                     | 38     | O 20 mg + A 1g bid, 5d; O 20 mg + A 1g + C 500 mg + M 500 mg, bid, 5d | Concomitant therapy (O 20 mg + A 1g + C 500 mg + M 500 mg, bid, 10d) | RUT, UBT, histology, or culture                          | UBT 4w                                        | 3            |             |
| Heo et al[26](2015) | Korea        | RCT          | 422             | 57                     | 59     | E 20 mg + A 1g bid, 7d; E 20 mg + A 1g + C 500 mg + M 500 mg, bid, 5d | Concomitant therapy (E 20 mg + A 1g + C 500 mg + M 500 mg, bid, 5d) | Any two of UBT, histology, or RUT                        | UBT 4w                                        | 3            |             |
| Hwang et al[29](2015) | Korea        | RCT          | 284             | 59                     | 46     | R 20 mg + A 1g bid, 7d; R 20 mg + A 1g + C 500 mg + M 500 mg, bid, 5d | Sequential therapy (R 20 mg + A 1g, bid, 7d; R 20 mg + M 500 mg, bid, Mo 500 mg, qd, 7d or 14d) | UBT, histology, or RUT                                | UBT 4w                                        | 3            |             |
| Chen et al[30](2015) | Taiwan       | RCT          | 175             | 53                     | 37     | R 20 mg + A 1g bid, 7d; R 20 mg + A 1g + C 500 mg + M 500 mg, bid, 7d | Sequential therapy (R 20 mg + A 1g, bid, 7d; R 20 mg + C 500 mg + M 500 mg, bid, 5d) | RUT + histology, or culture                            | UBT 8w                                        | 2            |             |
| Metanat et al[31](2015) | Iran         | RCT          | 270             | 46                     | 44     | P 40 mg + A 1g bid, 7d; P 40 mg + A 1g + C 500 mg + T 500 mg, bid, 7d | Concomitant therapy (P 40 mg + A 1g bid, 7d; P 40 mg + A 1g + C 500 mg + T 500 mg, bid, 5d) | UBT, histology                                      | UBT 8w                                        | 2            |             |

A: Amoxicillin; C: Clarithromycin; E: Esomeprazole; M: Metronidazole; Mo: Moxifloxacin; N: Nitroimidazole; O: Omeprazole; P: Pantoprazole; R: Rabeprazole; RUT: Rapid urease test; T: Tinidazole; UBT: 13C-urea breath test.
The characteristics of included studies are shown in Table 1. In the quality assessment, the blinding item was least fulfilled as no study used placebo or declared blinding to treatment regimen for patients or researchers. Except for three RCTs [11,12,24], most RCTs described the method of randomization. All studies clearly presented the follow-up data and conducted ITT analysis.

Overall eradication rate of hybrid therapy
The eradication rate was reported in 12 studies. In PP analysis, the overall eradication rate was 91.2% (88.5%-93.4%), with significant heterogeneity ($I^2 = 63.9\%, P < 0.05$). In subgroup analyses, the pooled rate was 91.1% (87.4%-93.8%) for 10 studies using the 14-d regimen, and 90.3% (84.6%-94.1%) for 4 studies using the 10-d regimen (Figure 2A). In ITT analysis, the pooled eradication rate was 85.2% (82.1%-87.8%). For 10-d regimen (4 records) and 14-d regimen (10 records), the pooled rate was 82.2% (75.7%-87.2%) and 86.5% (82.6%-89.7%), respectively.

Different durations of hybrid therapy
Only two RCTs compared the hybrid therapies lasting 10 and 14 d, respectively [23,24]. In PP analysis, the 14-d compliance patients or withdrawals were included in the ITT analysis to minimize bias [19]. Sensitivity analysis was performed by excluding the studies one by one. Subgroup analyses were conducted by stratifying the duration of therapy. The publication bias was assessed by the Egger's test and the funnel plot. $P < 0.05$ was considered statistically significant.
A

| Group by Duration | Study name          | Event rate | Lower limit | Upper limit |
|--------------------|---------------------|------------|-------------|-------------|
| 10d                | Wu et al (2014)a    | 0.950      | 0.856       | 0.984       |
| 10d                | Cuadrado-Lavin et al (2015) | 0.939    | 0.878       | 0.971       |
| 10d                | Heo et al (2015)    | 0.896      | 0.846       | 0.931       |
| 10d                | Metanat et al (2015)b | 0.839    | 0.763       | 0.894       |
| 10d                | Wu et al (2014)b    | 0.951      | 0.858       | 0.984       |
| 12d                | Wu et al (2014)c    | 0.950      | 0.856       | 0.984       |
| 14d                | Heu et al (2011)    | 0.991      | 0.938       | 0.999       |
| 14d                | Saradarian et al (2012) | 0.871    | 0.819       | 0.910       |
| 14d                | Molina-Infante et al (2013) | 0.920    | 0.867       | 0.953       |
| 14d                | Zullo et al (2013)  | 0.857      | 0.765       | 0.917       |
| 14d                | De Francesco et al (2014) | 0.958    | 0.897       | 0.984       |
| 14d                | Oh et al (2014)     | 0.859      | 0.768       | 0.918       |
| 14d                | Wu et al (2014)c    | 0.950      | 0.856       | 0.984       |
| 14d                | Hwang et al (2015)  | 0.826      | 0.754       | 0.881       |
| 14d                | Chen et al (2015)   | 0.964      | 0.895       | 0.988       |
| 14d                | Metanat et al (2015)a | 0.929    | 0.868       | 0.962       |
| 14d                | Wu et al (2014)b    | 0.950      | 0.856       | 0.984       |
| Overall            |                    | 0.912      | 0.885       | 0.934       |

B

| Study ID | RR (95%CI) | % Weight |
|----------|------------|----------|
| 14d vs 10d | 1.15 (1.05, 1.26) | 17.07 |
| Saradarian et al (2012) | 0.93 (0.84, 1.03) | 16.16 |
| Zullo et al (2013) | 1.02 (0.95, 1.08) | 18.84 |
| De Francesco et al (2014) | 1.18 (1.06, 1.31) | 15.97 |
| Chen et al (2015) | 1.06 (0.96, 1.18) | 68.03 |
| Subtotal (I-squared = 80.5%, P = 0.002) | | |
| 14d vs 14d | 1.05 (0.92, 1.19) | 14.57 |
| Hwang et al (2015) | 0.88 (0.8, 0.96) | 17.40 |
| Subtotal (I-squared = 79.9%, P = 0.026) | | |
| Overall (I-squared = 82.2%, P = 0.000) | 1.03 (0.94, 1.12) | 100.00 |
| Note: Weights are from random effects analysis | | |

C

| Study ID | RR (95%CI) | % Weight |
|----------|------------|----------|
| 14d vs 14d | 0.96 (0.91, 1.01) | 21.09 |
| De Francesco et al (2014)a | 1.01 (0.95, 1.07) | 19.53 |
| Subtotal (I-squared = 35.7%, P = 0.212) | 0.98 (0.93, 1.03) | 40.62 |
| 14d vs 5d | 0.94 (0.84, 1.04) | 11.07 |
| De Francesco et al (2014)b | 1.12 (1.03, 1.23) | 13.55 |
| Subtotal (I-squared = 84.7%, P = 0.010) | 1.03 (0.86, 1.23) | 24.62 |
| 10d vs 10d | 1.04 (0.96, 1.12) | 16.35 |
| Heo et al (2015) | 1.00 (0.93, 1.07) | 18.41 |
| Subtotal (I-squared = 0.0%, P = 0.416) | 1.02 (0.97, 1.07) | 34.76 |
| Overall (I-squared = 56.1%, P = 0.044) | 1.01 (0.96, 1.05) | 100.00 |
| Note: Weights are from random effects analysis | | |

Figure 2 Per-protocol analysis. Forest plot showing the overall eradication rate of Helicobacter pylori (H. pylori) using hybrid therapy based on data from PP analysis. Subgroup analyses were conducted based on different durations of hybrid regimen. B: Forest plot comparing hybrid with sequential therapy in H. pylori eradication using data from PP analysis. Subgroup analyses were conducted based on different durations of sequential regimen. C: Forest plot comparing hybrid with concomitant therapy in H. pylori eradication using the data from PP analysis. Subgroup analyses were conducted based on different durations of concomitant regimen.
The regimen did not show significantly higher eradication rate compared with 10-d regimen (RR = 1.04, 95%CI: 0.92-1.18, P > 0.05). Significant heterogeneity was presented (I² = 73.4%, P = 0.05). In ITT analysis, no significant superiority was found for the 14-d regimen compared with the 10-d regimen (RR = 1.08, 95%CI: 0.99-1.19, P > 0.05), without heterogeneity (I² = 0%, P > 0.05).

**Hybrid therapy vs sequential therapy**

Eradication rate: Six studies were available [11-14,25,26]. Two Korean RCTs [13,26] and 2 Italian RCTs [12,14] were conducted by the same groups, during different study periods. In PP analysis, the eradication rate was 88.6% (95%CI: 83.6%-92.3%) for hybrid therapy and 87.8% (95%CI: 79.9%-92.9%) for sequential therapy. No statistically significant difference was found between the hybrid and sequential therapies, with significant heterogeneity (RR = 1.03, 95%CI: 0.94-1.12, P = 0.59; I² = 82.2%, P < 0.05) (Figure 2B). In ITT analysis, the eradication rate was 84.3% (95%CI: 79.3%-88.2%) for hybrid therapy and 85.1% (95%CI: 78.4%-89.9%) for sequential therapy. No significant differences were seen with hybrid therapy compared with sequential therapy (RR = 1.00, 95%CI: 0.89-1.12, P = 0.94). Significant heterogeneity was found (I² = 85.2%, P < 0.05) (Table 2).

Sensitivity analyses were carried out by excluding the studies one by one. Notably, no significant change was shown for PP or ITT results. Regarding sequential therapy, 4 studies used the 10-d regimen [11,12,14,25] and 2 studies used the 14-d regimen [13,26]. Based on the different durations, subgroup analysis of PP data did not find statistically significant changes for the 10-d regimen (RR = 1.06, 95%CI: 0.96-1.18) or for the 14-d regimen (RR = 0.95, 95%CI: 0.80-1.13) (Figure 2B). Similarly, subgroup analysis of ITT data revealed no significant alteration for the 10-d regimen (RR = 1.03, 95%CI: 0.88-1.20) or for the 14-d regimen (RR = 0.93, 95%CI: 0.79-1.09).

**Compliance:** Five studies evaluated the compliance [11,13,14,25,26]. Both therapies displayed a high compliance rate [96% (95%CI: 93%-98%)] for hybrid therapy, and 98% (95%CI: 95%-99%) for sequential therapy. No significant difference was observed (RR = 0.99, 95%CI: 0.96-1.02, P = 0.55; I² = 50.4%, P > 0.05) (Table 2).

**Side effects:** The overall adverse effect rate was 30.3% (95%CI: 20.9%-41.6%) for the hybrid therapy, and 28.2% (95%CI: 15.7%-45.4%) for the sequential therapy.

---

**Table 2** Summary of meta-analyses: hybrid therapy vs sequential and concomitant therapy

| Outcomes                  | Studies, n | Hybrid group | Control group | RR (95%CI) | I²  | P value for heterogeneity |
|---------------------------|------------|--------------|---------------|------------|-----|--------------------------|
| Hybrid vs sequential      |            |              |               |            |     |                          |
| Eradication rate (PP)     | 6          | 88.6%        | 87.8%         | 1.03 (0.94-1.12) | 82.2% | < 0.05                 |
| Eradication rate (ITT)    | 6          | 84.3%        | 85.1%         | 1.00 (0.89-1.12) | 85.2% | < 0.05                 |
| Compliance                | 5          | 96.0%        | 98.0%         | 0.99 (0.96-1.02) | 50.4% | > 0.05                 |
| Side effect rate          | 6          | 30.3%        | 28.2%         | 1.05 (0.86-1.02) | 37.8% | > 0.05                 |
| Hybrid vs concomitant     |            |              |               |            |     |                          |
| Eradication rate (PP)     | 5          | 91.3%        | 92.4%         | 1.01 (0.96-1.05) | 56.1% | < 0.05                 |
| Eradication rate (ITT)    | 5          | 84.8%        | 86.7%         | 0.99 (0.95-1.03) |    0 | > 0.05                 |
| Compliance                | 4          | 95.8%        | 93.2%         | 1.03 (1.00-1.05) | 7 | > 0.05                 |
| Side effect rate          | 4          | 39.5%        | 44.2%         | 0.93 (0.82-1.05) |    0 | > 0.05                 |

*Statistically significant results. ITT: Intention-to-treat; PP: Per-protocol.*
therapy. The hybrid therapy did not show significantly lower incidence of adverse effect (RR = 1.05, 95%CI: 0.86-1.02, \( P = 0.63 \)). No significant heterogeneity was observed (\( I^2 = 37.8\%, P > 0.05 \)) (Table 2).

**Hybrid therapy vs concomitant therapy**

**Eradication rate:** Five studies were available\(^{12,14,27-29}\). In PP analysis, the eradication rate of hybrid and concomitant regimen was 91.3% (95%CI: 87.7%-93.9%) and 92.4% (95%CI: 89.2%-94.7%), respectively. In ITT analysis, the eradication rate of hybrid and concomitant regimen was 84.8% (95%CI: 78.9%-89.2%) and 86.7% (95%CI: 80.7%-91.0%), respectively. In PP analysis, no statistically significant difference was observed between hybrid therapy and concomitant therapy (RR = 1.01, 95%CI: 0.96-1.05, \( P = 0.76; I^2 = 56.1\%\), \( P < 0.05 \)) (Figure 2C). In ITT analysis, no significant difference was found between the two regimens, and no heterogeneity was observed (RR = 0.99, 95%CI: 0.95-1.03, \( P = 0.47; I^2 = 0\%\), \( P > 0.05 \)) (Table 2).

In sensitivity analysis by excluding studies one by one, no significant change was seen in PP or ITT analysis. For concomitant therapy, two studies presented results of the 14-d regimen\(^{12,27}\), 2 of the 10-d regimen\(^{28,29}\), and 2 of the 5-d regimen\(^{12,14}\). Subgroup analyses based on different durations of concomitant therapy revealed no significant difference.

**Compliance:** Four studies were relevant\(^{14,27-29}\). The compliance rate was 95.8% (95%CI: 93.2%-97.4%) for hybrid therapy, and 93.2% (95%CI: 89.7%-95.6%) for concomitant therapy. Patients receiving hybrid therapy showed significantly higher rate of compliance when compared with concomitant therapy (RR = 1.03, 95%CI: 1.00-1.05, \( P < 0.05 \)). No heterogeneity was revealed (\( I^2 = 0\%\), \( P > 0.05 \)) (Table 2).

**Side effects:** Four studies were included\(^{12,14,27,28}\). The overall side effect rate was 39.5% (95%CI: 21.7%-60.7%) for hybrid therapy, and was 44.2% (95%CI: 26.7%-63.2%) for concomitant therapy. No significant difference was seen between hybrid therapy and concomitant therapy (RR = 0.93, 95%CI: 0.82-1.05, \( P = 0.24 \)). No heterogeneity was observed (\( I^2 = 0\%\), \( P > 0.05 \)) (Table 2).

**Publication bias**

Publication bias was representatively evaluated for PP data. For hybrid vs sequential therapy, the funnel plot was symmetrical, with a non-significant result in Egger’s test (\( P = 0.74 \)) (Figure 3A). In hybrid vs concomitant therapy, the funnel plot was symmetrical (Figure 3B). No statistical significance was revealed by Egger’s test (\( P = 0.48 \)).

**DISCUSSION**

Eradication rate plays a pivotal role in evaluating the success of \textit{H. pylori} treatment. The efficacy of \textit{H. pylori} eradication was graded as follows: (1) excellent (> 95%); (2) good (90-95%); (3) fair (85-89%); (4) bad (81%-84%); and (5) unacceptable (< 80%)\(^{30}\). In ITT and PP analyses, therapeutic significance was achieved when the eradication rates exceeded 80% and 90%, respectively\(^{26}\). In this meta-analysis, hybrid therapy yielded a good eradication rate (91%) in PP analysis, and fair (85%) in ITT analysis, both exhibiting significant therapeutic values. The pooled data showed similar treatment success (an eradication rate closer to 90%) with hybrid, sequential, and concomitant therapies against \textit{H. pylori}. Hybrid therapy had good compliance to medications, which was similar to sequential therapy and slightly better than concomitant therapy. The differences in adverse event rates were small between hybrid, sequential, and concomitant therapies. All the three therapies showed acceptable safety profile. The 10-d hybrid regimen did not show significant inferiority with respect to the eradication rate. Meta-analyses have shown that the eradication outcome was duration dependent\(^{9}\). However, the differences in eradication rate across all subgroups stratified by duration were minimal.

Currently, in the absence of any new drugs against \textit{H. pylori}, different combination regimens, including sequential, concomitant, and hybrid therapies, have been investigated extensively. Hybrid therapy evolved from sequential therapy and concomitant therapy. Compared with sequential therapy, hybrid therapy extended the duration of amoxicillin. Prolonging the duration of traditional triple therapy from 7 to 10-14 d improved the eradication success rate by approximately 5%\(^{2}\). The prescription of PPI and amoxicillin was similar for concomitant and hybrid therapies. However, clarithromycin and metronidazole were used over a shorter duration of hybrid therapy. The adverse effects of metronidazole included nausea and regurgitation. Furthermore, both metronidazole and clarithromycin may cause bitter tastes\(^{29}\). With decreased pill burden, hybrid therapy was superior in cost-effectiveness over concomitant therapy.

The participants included in the RCTs were residents of Taiwan, Iran, Italy, Spain, and Korea, which represent regions with a high prevalence of antibiotic-resistant \textit{H. pylori} strains\(^{5,11}\). Worldwide increase of \textit{H. pylori} resistance to antibiotics, especially clarithromycin and metronidazole, is the most important determinant of eradication failure in traditional triple therapy\(^{31}\). For sequential therapy, the eradication rate of clarithromycin-resistant and metronidazole-resistant strains was 72.8% and 86.4%, respectively. However, the rate decreased to just 37% for dual-resistant strains\(^{32}\). Concomitant regimen outperformed sequential regimen in areas with a high incidence of clarithromycin and/or metronidazole resistance\(^{33,34}\). However, eradication was expected to fail (< 90%) when the prevalence of dual clarithromycin-metronidazole resistant strains was > 15%\(^{34}\). Compared with concomitant therapy, hybrid
therapy initially prescribed amoxicillin, which may prevent the occurrence of secondary clarithromycin resistance\(^35,36\). Compared with sequential therapy, hybrid regimen extended the duration of amoxicillin exposure. Hybrid therapy combined the advantages of sequential and concomitant therapy. Unfortunately, very few studies conducted antimicrobial susceptibility testing before hybrid treatment. Chen et al\(^11\) showed that sequential therapy resulted in a 71.4% (5/7) eradication rate in patients harboring strains with dual resistance. Hybrid therapy yielded a 100% (4/4) eradication rate. Molina-Infante et al\(^34\) revealed that for clarithromycin-resistant and dual-resistant strains, the concomitant regimen resulted in a 100% (8/8 and 3/3, respectively) eradication rate. By contrast, hybrid therapy only achieved a rate of 75% (6/8) and 33% (1/3), respectively. Nevertheless, the very small number of patients with resistant strains precluded definite conclusions.

Our meta-analysis represented the most comprehensive review of hybrid therapy and an update of two similar meta-analyses\(^21,22\). Notably, five studies have only recently been published, which were not included in previous meta-analyses\(^11,24,26,28,29\). The number of studies for meta-analysis doubled that of the previous studies, generating more robust conclusions, albeit with similar non-significant results between different regimens. Additionally, it was the first time that hybrid therapy was compared with different durations of sequential or concomitant therapy. The overall eradication rate with durations of hybrid therapy was demonstrated.

This study had several limitations. The number of included trials was still small, and the sample size was not large enough for the majority of studies. For example, although we did not detect the impact of different durations of sequential or concomitant therapy, the results should be extrapolated with caution as only few studies were included. Most RCTs did not report blinding to treatment regimen. Lack of blinding may influence compliance and the reporting of side effects. The quality of included studies was low. The majority of studies did not conduct susceptibility tests to determine antibiotic resistance\(^12,25,28\). In fact, we have tried to assess the eradication efficacy in resistant strains. However, we had insufficient related data and very small sample sizes of resistant patients. A number of confounding factors may play a role in determining the \(H. \text{ pylori}\) eradication rates. Except for the disparity between different regions regarding the prevalence of resistant strains, the rates were influenced by genetic differences in the PPIs metabolism, degree of gastritis, administration of probiotics, and the nature of the underlying disease\(^23\). Additionally, different types of PPIs and nitroimidazole medications, and varying duration of follow-up may potentially generate small amounts of bias\(^27,28\). Participation in an RCT enhanced the patient compliance, and the compliance gap between hybrid therapy and other treatment regimens might be wider in clinical practice\(^29\).

In conclusion, hybrid therapy yielded good eradication efficacy for \(H. \text{ pylori}\) in regions with a high prevalence of antibiotic-resistant strains. Hybrid regimens achieved equivalent eradication rates compared with sequential or concomitant therapy. The compliance and adverse events were not different between hybrid, sequential or concomitant therapies. The 14-d and 10-d hybrid therapy showed similar eradication rates. Further studies are urgently required to clarify important differences in eradication of \(H. \text{ pylori}\) in the setting of varying patterns of antibiotic resistance.

**REFERENCES**

1. Yazbek PB, Trindade AB, Chin CM, Dos Santos JL. Challenges to the Treatment and New Perspectives for the Eradication of Helicobacter pylori. *Dig Dis Sci* 2015; 60: 2901-2912 [PMID: 25999247 DOI: 10.1007/s10620-015-3712-y]
2. Malfertheiner P, Megraud F, O’Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Ginsbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. *Gut* 2012; 61: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]
3. Liu JM, Chen CC, Chen MJ, Chen CC, Chang CY, Fang YJ, Lee YJ, Hsu SJ, Luo JC, Chang WH, Hsu YC, Tseng CH, Tseng PH, Wang HP, Yang UC, Shen CT, Lin JT, Lee YC, Wu MS. Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial.
Song ZQ et al. Hybrid therapy for H. pylori eradication.

Lancet 2013; 381: 205-213 [PMID: 23158886 DOI: 10.1016/S0140-6736(12)61579-7]

Li BZ, Threaderone DE, Wang JY, Xu JM, Yuan QJ, Zhang C, Li P, Ye QL, Guo B, Mao C, Ye DQ. Comparative effectiveness and tolerance of treatments for Helicobacter pylori: systematic review and network meta-analysis. BMJ 2015; 351: h4052 [PMID: 26290044 DOI: 10.1136/bmj.h4052]

Megaraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Glupczynski Y. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013; 62: 34-42 [DOI: 10.1136/gutjnl-2012-302254]

Zullo A, Vaira D, Vakil N, Hassan C, Gatta L, Ricci C, De Francesco V, Menegatti M, Tampieri A, Perna F, Rinaldi V, Perri F, Papadìa C, Fornari F, Pilati S, Mete LS, Merla A, Poti R, Marinnone G, Savioli A, Campo SM, Falco D, Ierardi E, Miglioli M, Morini S. High eradication rates of Helicobacter pylori with a new sequential treatment. Aliment Pharmacol Ther 2007; 15: 719-726 [PMID: 17046522 DOI: 10.1111/j.1365-2036.2003.01461.x]

Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential, concomitant and hybrid first-line therapies for Helicobacter pylori: an open-label, randomized, multicentre clinical trial. World J Gastroenterol 2015; 21: 10435-10442 [PMID: 26420970 DOI: 10.3748/wjg.v21.i36.10435]

Hsu PI, Wu DC, Graham DY, Wang WM. Feasibility of shortening 14-day hybrid therapy while maintaining an excellent Helicobacter pylori eradication rate. Helicobacter 2014; 19: 207-213 [PMID: 24612093 DOI: 10.1111/hel.12113]

Metanet HA, Valizadeh SM, Fakheri H, Maleki I, Taghvai T, Hosseini V, Bari Z. Comparison Between 10- and 14-Day Hybrid Regimens for Helicobacter pylori Eradication: A Randomized Clinical Trial. Helicobacter 2015; 20: 299-304 [PMID: 25752357 DOI: 10.1111/hel.12202]

Sardarian H, Fakheri H, Hosseini V, Taghvai T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for Helicobacter pylori eradication in Iran: a prospective randomized trial. Helicobacter 2013; 18: 129-134 [PMID: 23121338 DOI: 10.1111/hel.12017]

Hwang JJ, Lee DH, Yoon H, Shin CM, Park YS, Kim N. Efficacy of moxifloxacin-based sequential and hybrid therapy for first-line Helicobacter pylori eradication. World J Gastroenterol 2015; 21: 10234-10241 [PMID: 26401089 DOI: 10.3748/wjg.v21.i35.10234]

Molina-Infante J, Romano M, Fernandez-Bermejo M, Federico A, Gravina AV, Pozzati L, Garcia-Abadia E, Vinagre-Rodriguez G, Martinez-Alcalá C, Hernandez-Alonso M, Miranda A, Iovene MR, Pazos-Pacheco C, Gisbert JP. Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in populations with high rates of antibiotic resistance. Gastroenterology 2013; 145: 121-128.e1 [PMID: 23562754 DOI: 10.1053/j.gastro.2013.03.050]

Cuadrado-Lavin A, Salcines-Caviedes JR, Diaz-Perez A, Carrascosa MF, Ochagavia M, Fernandez-Forceldelo JL, Cobo M, Fernandez-Gil P, Ayestaran B, Sánchez B, Campo C, Illoca J, Lorenzo S, Illaro A. First-line eradication rates comparing two shortened non-bismuth quadruple regimens against Helicobacter pylori: an open-label, randomized, multicentre clinical trial. J Antimicrob Chemother 2015; 70: 2376-2381 [PMID: 25855760 DOI: 10.1093/jac/dkv099]

Heo J, Jeon SW, Jung JT, Kwon JG, Lee DW, Kim HS, Yang CH, Park JB, Park KS, Cho KB, Lee SH, Jang BI. Concomitant and hybrid therapy for Helicobacter pylori infection: A randomized controlled trial. J Gastroenterol Hepatol 2015; 30: 1361-1366 [PMID: 25867608 DOI: 10.1111/jgh.12983]

Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. Helicobacter 2007; 12: 275-278 [PMID: 17669098 DOI: 10.1111/j.1365-2376.2007.00518.x]

Papastergiou V, Georgopoulos SD, Karatapanis S. Treatment of Helicobacter pylori infection: meeting the challenge of antimicrobial resistance. World J Gastroenterol 2014; 20: 9898-9911 [PMID: 25104200 DOI: 10.3748/wjg.v20.i29.9898]

Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. BMJ 2013; 347: 64587 [PMID: 23926315 DOI: 10.1136/bmj.f4587]

Kim JS, Park SM, Kim BW. Sequential or concomitant therapy for eradication of Helicobacter pylori infection: A systematic review
and meta-analysis. *J Gastroenterol Hepatol* 2015; 30: 1338-1345 [PMID: 25867718 DOI: 10.1111/jgh.12984]

34 **Molina-Infante J**, Gisbert JP. Optimizing clarithromycin-containing therapy for *Helicobacter pylori* in the era of antibiotic resistance. *World J Gastroenterol* 2014; 20: 10338-10347 [PMID: 25132750 DOI: 10.3748/wjg.v20.i30.10338]

35 **Zullo A**, De Francesco V, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. *Gut* 2007; 56: 1353-1357 [PMID: 17566020 DOI: 10.1136/gut.2007.125658]

36 **Murakami K**, Fujioka T, Okimoto T, Sato R, Kodama M, Nasu M. Drug combinations with amoxicillin reduce selection of clarithromycin resistance during *Helicobacter pylori* eradication therapy. *Int J Antimicrob Agents* 2002; 19: 67-70 [PMID: 11814770 DOI: 10.1016/S0924-8579(01)00456-3]

37 **Vakil N**. Are there geographical and regional differences in *Helicobacter pylori* eradication? *Can J Gastroenterol* 2003; 17 Suppl B: 30B-32B [PMID: 12845348]
