A Pilot Randomized Controlled Study of Dexlansoprazole MR-Based Triple Therapy for *Helicobacter pylori* Infection

Deng-Chyang Wu, MD, PhD, Chao-Hung Kuo, MD, PhD, Feng-Woei Tsay, MD, Wen-Hung Hsu, MD, PhD, Angela Chen, PhD, and Ping-I Hsu, MD

Abstract: Dexlansoprazole MR is the R-enantiomer of lansoprazole that is delivered by a dual delayed release formulation. It is effective for symptom control of patients with gastroesophageal reflux disease. However, its efficacy in the treatment of *Helicobacter pylori* infection remains unclear. This pilot, randomized, controlled, head-to-head study was conducted to investigate whether the efficacy of single-dose dexlansoprazole MR-based triple therapy was noninferior to double-dose rabeprazole-based triple therapy in the treatment of *H pylori* infection.

Consecutive *H pylori*-infected subjects were randomly allocated to either 7-day dexlansoprazole MR-based standard triple therapy (dexlansoprazole MR 60 mg once daily, clarithromycin 500 mg twice daily, and amoxicillin 1 g twice daily) or rabeprazole-based triple therapy (rabeprazole 20 mg twice daily, clarithromycin 500 mg twice daily, and amoxicillin 1 g twice daily). *H pylori* status was assessed 6 weeks after the end of treatment.

A total of 177 *H pylori*-infected patients were randomized to receive dexlansoprazole MR-based (n = 90) or rabeprazole-based (n = 87) triple therapy. Intention-to-treat analysis demonstrated no differences between eradication rates of the 2 study groups (83.3% vs 81.6%; \( P = 0.736 \)). Per-protocol analysis yielded comparable results (85.1% vs 81.2%; \( P = 0.497 \)). Both groups exhibited similar frequencies of adverse events (7.8% vs 4.6%; \( P = 0.536 \)) and drug compliance (98.9% vs 97.7%; \( P = 0.496 \)). Multivariate analysis disclosed that the presence of clarithromycin resistance was the only independent factors predictive of treatment failure with an odds ratio of 6.8 (95% confidence interval: 1.2–37.6).

This work demonstrates that single-dose dexlansoprazole MR-based triple therapy yields a similar eradication rate as double-dose rabeprazole-based therapy. Since the pharmaceutical cost of the single-dose dexlansoprazole MR regime is lower than that of the double-dose rabeprazole regimen, dexlansoprazole-based therapy can reasonably be recommended in the first-line treatment of *H pylori* infection.

Editor: Bulent Kantarceken.

Received: July 3, 2015; revised: January 10, 2016; accepted: January 14, 2016.

From the Division of Gastroenterology (D-CW, W-HH), Department of Internal Medicine, Kaohsiung Medical University Hospital; Division of Internal Medicine (D-CW), Kaohsiung Municipal Ta-Tung Hospital; Department of Internal Medicine and Cancer Center (D-CW), Kaohsiung Medical University Hospital; Cancer for Stem Cell Research (D-CW), Department of Internal Medicine, Kaohsiung Medical University Hospital; Division of Gastroenterology (D-CW), Kaohsiung Medical University; Division of Gastroenterology (F-WT, P-IH), Kaohsiung Veterans General Hospital and National Yang-Ming University; and Institute of Biomedical Sciences (AC), National Sun Yat-Sen University, Kaohsiung, Taiwan.

Correspondence: Ping-I Hsu, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, 386 Ta Chung 1st Road, Kaohsiung 813, Taiwan, R.O.C.

Guarantor of the article: D-CW.

D-CW, P-IH, drafting of the manuscript; critical revision of the manuscript for important intellectual content and take responsibility for the integrity of the data and the accuracy of the data analysis, C-HK, F-WT, AC contributed in study design, acquisition of data, and statistical analysis; all authors contributed in data interpretation and manuscript preparation. This study was supported by grants from National Science Council of the ROC (NSC 101-2314-B-075-002-MY2), Kaohsiung Medical University “Aim for the Top Universities Grant” (grant No. KMU-TP104G00, KMU-TP104G03), and Kaohsiung Medical University Hospital (KMUH101-IR01, KMUH100-0101). The authors have no conflicts of interest to disclose. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved. This is an open access article distributed under the Creative Commons Attribution License 4.0, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. ISSN: 0025-7974. DOI: 10.1097/MD.0000000000002698

**INTRODUCTION**

*Helicobacter pylori* infects more than 50% of the adult population globally. The bacterium induces chronic inflammation of gastric mucosa and leads to various gastrointestinal diseases, such as peptic ulcer, gastric adenocarcinoma, and mucosa-associated tissue lymphoma.1,2 Currently, *H pylori* eradication has become the standard treatment to cure peptic ulcer disease.3,4 This therapy is also advocated in the treatment of *H pylori*-related mucosa associated lymphoid tissue lymphoma.5 In regions with high incidence of gastric cancer, *H pylori* eradication is recommended for the prevention of cancer development.6,7

Proton pump inhibitor (PPI) is one of the key medicines in anti-*H pylori* regimens. It possesses anti-*H pylori* activity,8 and also increases bioavailability and activity of some antibiotics by reducing gastric acid secretion.9 Dexlansoprazole, an R-enantiomer of lansoprazole, is a PPI with a dual delayed release formulation providing effective plasma drug concentration.11 The dual delayed release–time curve (AUC), and a longer elimination half-life than *S*-lansoprazole.10 Dexlansoprazole modified release (MR) is a novel PPI with a dual delayed release formulation providing 2 separate releases of medication to extend the duration of effective plasma drug concentration.11 The dual delayed release PPI possesses 2 types of enteric-coated granules with different pH-dependent dissolution characteristics to release an initial drug in the proximal small intestine, at a pH of approximately 5.5, followed several hours later by another drug release at distal small intestine, at a pH of ≥6.0.12 It is effective in improving the healing of erosive esophagitis and in the treatment of symptomatic gastroesophageal reflux disease.13–15 However, its efficacy in the treatment of *H pylori* infection remains unclear.

Our previous study demonstrated that esomeprazole-based triple therapy achieved a higher eradication rate than pantopra-zole-based regimen.16 The difference in eradication efficacies between the 2 study groups is most likely due to the more powerful acid inhibition effect of esomeprazole compared with...
pantoprazole. A recent cross-over study documented that esomeprazole at standard dose of 40 mg once daily provides more effective control of gastric acid than standard doses of pantoprazole, lansoprazole, and rabeprazole. A comparison study of dexlansoprazole 60 mg with esomeprazole 40 mg showed that dexlansoprazole MR 60 mg achieved a greater acid control than esomeprazole 40 mg (the mean percentage of time with pH >4 between 0 to 24 hours post-dose: 58% and 48%, respectively). Since single-dose esomeprazole (40 mg daily)-based triple therapy has been shown to achieve a similar eradication rate as double-dose esomeprazole (40 mg b.d.)-based therapy, dexlansoprazole MR is potentially a promising PPI which can be used in H pylori eradication.

Currently, the efficacy of dexlansoprazole MR-based standard triple therapy is still lacking. We therefore conducted this pilot study to assess the eradication rate of dexlansoprazole MR-based triple therapy for H pylori infection, and to investigate whether the efficacy of single-dose dexlansoprazole MR-based triple therapy is noninferior to double-dose rabeprazole-based triple therapy in the treatment of H pylori infection.

**METHODS**

Patients

This study was a prospective, noninferiority, randomized, controlled trial. Consecutive adult patients with endoscopically proven H pylori-related peptic ulcer diseases or gastritis were recruited for the study. The diagnosis of H pylori was based on at least 2 positive results of histology, rapid urease test, and culture. Criteria for exclusion criteria were as follows: age younger than 20 years; previous H pylori-eradication therapy, ingestion of antibiotics or bismuth within the prior 4 weeks, presence of severe comorbidities, allergy to any of the medications used in the trial, and pregnant woman. The study protocol was approved by the Ethics Committee of the Kaohsiung Medical University Hospital (IRB number: KMUH-IRB-E (I)-20150107). It was registered as a standard randomized Clinical Trial (ClinicalTrials.gov identifier: NCT02541786).

Randomization and Treatment

We randomly allocated patients at a 1:1 ratio to receive either a DCA (dexlansoprazole MR [Dexilant delayed release; Takeda, Osaka, Japan] 60 mg once daily, clarithromycin 500 mg twice daily, and amoxicillin 1 g twice daily) or RCA (rabeprazole [Panet; Eisai, Misato, Japan] 20 mg twice daily, clarithromycin 500 mg twice daily, and amoxicillin 1 g twice daily) therapy according to a computer-generated number sequence. All medicines were taken 1 hour before breakfast and dinner. The random number sequence was generated by an independent study assistant. The treatment allocation was concealed in an opaque envelope until anti-H pylori therapy was assigned. After informed consents were obtained from the participants, a study nurse assigned anti-H pylori therapies according to the treatment allocations in the envelopes.

Study Design

All recruited patients were requested to complete a questionnaire that contained questions regarding demographic data and history of smoking, alcohol drinking, nonsteroidal anti-inflammatory drug use, and underlying diseases. The patients were informed of the common adverse events of anti-H pylori therapy and were requested to record the side effects during treatment. The severity of adverse events was recorded according to a 4-point scale (none; mild; moderate; severe) system as previous description. Drug compliance was determined via pill counts. Good compliance was defined as participants taking at least 80% of eradication drugs, and poor compliance was defined as participants taking less than 80% of drugs.

Because a gastric cancer presenting with an ulcerative lesion might be missed by initial biopsy at endoscopy on enrollment, a follow-up endoscopy with histological examination, urease test, and culture was performed for the patients with gastric ulcers to assess the eradication outcome and the healing status of ulcers 6 weeks following anti-H pylori therapy. Patients with gastritis or duodenal ulcer underwent a urea breath test to assess final H pylori status. The urea breath test was conducted by a staff who was blind to the eradication arm. The cutoff value of urea breath test was set at 4.8% of 13C CO2. Cure of H pylori infection was defined as negative results of all histology, urease test and bacterial culture, or a negative result of urea breath test.

An antral gastric biopsy specimen was obtained for H pylori culture, using previously described methods. H pylori culture was performed by rubbing the specimens on the surface of a Campy-BAP agar plate (Brucella agar + IsoVitalex + 10% whole sheep blood). Then, they were incubated at 37°C with microaerobic condition for 4 to 5 days. The results of culture were regarded as positive if at least 1 colony of gram-negative bacilli with positive oxidase, catalase, and urease tests was found. The resistance to antibiotics was assessed by E-test (AB Biodisk, Solna, Sweden), and antibiotic resistances for clarithromycin, amoxicillin, and metronidazole were considered positive if the minimum inhibitory concentration values were >1, >0.5, and >8 μg/mL, respectively.

Statistical Analysis

The primary endpoint of the study was eradication rate of H pylori. It was evaluated by intention-to-treat (ITT) and per-protocol (PP) analyses. ITT analysis included all participants enrolled in the study regardless of drug compliance. Participants without follow-up tests for final H pylori status were assumed to have been treated unsuccessfully. PP analysis only included patients with good drug compliance who received follow-up examinations for eradication outcomes. The second outcomes were the frequency of adverse events and compliance to medications. Differences in baseline characteristics, eradication rates, and adverse events between groups were determined by χ2 test or Fisher exact test, as appropriate. The Student t test was used for the comparison of continuous data. SPSS (version 12.0 for Microsoft Windows) were used for all statistical analyses. A P value of <0.05 was regarded as significant difference.

According to our previous study, the eradication rate of standard triple therapy by conventional PPI is 82%. If there is a true difference in favor of the DCA treatment of 8%, at least 176 patients are required to be 90% sure that the upper limit of a 1-sided 95% confidence interval will exclude a difference in favor of the control group of more than 8%, assuming 10% loss to follow-up. Thirteen clinical and bacterial parameters including age, sex, smoking habit, alcohol consumption (<80 or >80 g/day), drug compliance, and antibiotic resistance were examined by univariate analysis to search the factors related to eradication rate. A stepwise logistic regression method was then applied to search the independent factors influencing eradication outcome.
RESULTS

Characteristics of the Study Groups

A total of 177 H pylori-infected participants were recruited for the study and randomly allocated to DCA (n = 90) or RCA (n = 87) therapy. The baseline demographic data and clinical parameters of the 2 treatment groups are listed in Table 1. There were no differences in all factors between groups. The flow of patients through the study is shown in Figure 1. In the recruited patients, 4 (DCA group: 2 patients; RCA group: 2 patients) with poor compliance and 1 (DCA group: 1 patient; RCA group: 0 patient) with incomplete follow-up were excluded from PP analysis.

Eradication of H Pylori

Table 2 shows the eradication rates of DCA and RCA groups. The eradication rate of DCA group was similar to that of RCA group by ITT analysis (83.3% vs 81.6%, \( P = 0.736 \)). Additionally, PP analysis also demonstrated that the DCA and RCA groups had comparable eradication rates (85.1% vs 81.2%, \( P = 0.497 \)).

Adverse Events and Compliances

Overall, 7.8% of the patients in the DCA group and 4.6% of those in the rabeprazole group suffered from at least 1 adverse event \( (P = 0.536) \). Table 3 lists the profiles of adverse events during eradication treatment. The 2 therapeutic groups shared similar adverse events during eradication therapy (Table 3). In the DCA group, 1 patient discontinued medicines owing to the development of skin rash. A patient in the rabeprazole group stopped treatment due to dizziness. The 2 treatment arms showed comparable compliance rates (97.8% vs 97.7%, \( P = 1.000 \)). Two patients in the DCA group and another 2 in the RCA group had poor drug compliance.

Factors Influencing Efficacy of Anti-H pylori Therapy

Univariate analysis showed that clarithromycin was a factor related to the eradication outcome \( (P = 0.046; \) Table 4). The other factors including smoking, alcohol consumption, type of PPI, and drug compliance did not influence eradication rate. Multivariate analysis confirmed that clarithromycin resistance was an independent factor determining eradication outcome of standard triple therapy \( (\text{odds ratio}: 6.75; 95\% \text{ CI}, 1.21–37.64; P = 0.029; \) Table 5).

DISCUSSION

In the current study, we conducted the first, head-to-head, randomized, controlled trial to investigate whether the efficacy of single-dose dexlansoprazole MR-based triple therapy was noninferior to double-dose rabeprazole-based triple therapy in the treatment of \( H \) pylori infection. Both ITT and PP analyses demonstrated that the eradication rate of dexlansoprazole MR-based triple therapy was similar to that of rabeprazole-based triple therapy (83.3% vs 81.6% and 85.1% vs 81.2%, respectively). Additionally, both therapies had similar frequencies of adverse events and drug compliance. The data clearly indicate that single-dose dexlansoprazole MR is noninferior to double-dose rabeprazole-base triple therapy in the treatment of \( H \) pylori infection.
Currently, lansoprazole 30 mg twice daily is widely used in clinical practice. In this study, single-dose of dexlansoprazole MR 60 mg daily was applied for H. pylori eradication. In terms of cost-effective view, the pharmaceutical costs of 7-day dexlansoprazole MR- and rabeprazole-based triple therapies in Taiwan were $19.4 and $20.4, respectively. The former was cheaper than the latter. Dexlansoprazole MR-based therapies can therefore be recommended in the first-line treatment of H. pylori infection for Taiwanese and probably most people in the world.

In the current study, the frequencies of adverse events in the dexlansoprazole-MR and rabeprazole group were 7.8% and 4.6%, respectively. The 2 therapeutic groups had comparable frequency of adverse events. Additionally, they shared similar drug compliance (97.8% vs 97.7%). In the dexlansoprazole MR group, 1 patient discontinued eradication therapy due to skin rash. On the other hand, a patient in the rabeprazole group stopped anti-H pylori therapy owing to severe dizziness.

The main reasons for eradication failure for H. pylori infection include antibiotic resistance, poor compliance, CYP2C19 genotypes, and smoking.25–27 In the current study, the eradication rate in the patients with clarithromycin-resistant strains was lower than that in those with clarithromycin-susceptible strains (66.7 vs 93.1%). Multivariate analysis

### TABLE 2. Major Outcomes of DCA and RCA Therapies

| Eradication Rate | DCA Therapy (n = 90) | RCA Therapy (n = 87) | P Value |
|------------------|---------------------|---------------------|---------|
| Intention-to-treat | 83.3% (75/90) (75.6%–91.0%) | 81.6% (71/87) (73.5%–89.7%) | 0.736 |
| Per-protocol | 85.1% (74/87) (77.6%–92.6%) | 81.2% (69/85) (72.9%–89.5%) | 0.497 |
| Adverse events | 7.8% (7/90) (2.3%–13.3%) | 4.6% (4/87) (0.2%–9.0%) | 0.536 |
| Compliance | 97.8% (88/90) (94.8%–100.8%) | 97.7% (85/87) (94.6%–100.8%) | 1.000 |

* 95% confidence interval.

### TABLE 3. Adverse Events During DCA and RCA Therapies

| Adverse Events | DCA Therapy (n = 90) | RCA Therapy (n = 87) | P Value |
|----------------|---------------------|---------------------|---------|
| Abdominal pain | 3 (2/1/0)* | 1 (1/0/0) | 0.621 |
| Constipation | 0 (0/0/0) | 0 (0/0/0) | — |
| Diarrhea | 1 (1/0/0) | 1 (1/0/0) | 1.000 |
| Dizziness | 1 (1/0/0) | 2 (1/0/1) | 0.617 |
| Headache | 0 (0/0/0) | 0 (0/0/0) | — |
| Anorexia | 0 (0/0/0) | 1 (1/0/0) | 0.492 |
| Nausea | 0 (0/0/0) | 0 (0/0/0) | — |
| Vomiting | 0 (0/0/0) | 0 (0/0/0) | — |
| Bad taste | 0 (0/0/0) | 1 (1/0/0) | 0.492 |
| Skin rash | 2 (0/1/1) | 1 (1/0/0) | 1.000 |
| Fatigue | 0 (0/0/0) | 2 (2/0/0) | 0.240 |
| other | 0 (0/0/0) | 0 (0/0/0) | — |

*The numbers of patients who suffered from mild, moderate, and severe adverse events.

### TABLE 4. Univariate Analysis of the Clinical Factors Influencing the Efficacy of DCA and RCA Therapies

| Principle Parameter | No of Patients | Eradication Rate | P Value |
|---------------------|----------------|-----------------|---------|
| Age | | | |
| <60 yr | 107 | 83.2% | 0.765 |
| ≥60 yr | 70 | 81.4% | |
| Sex | | | |
| Female | 97 | 80.4% | 0.424 |
| Male | 80 | 85.0% | |
| Smoking | | | |
| (−) | 155 | 81.9% | 0.770 |
| (+) | 22 | 86.4% | |
| Alcohol consumption | | | |
| (−) | 168 | 81.5% | 0.363 |
| (+) | 9 | 100% | |
| Ingestion of coffee | | | |
| (−) | 121 | 83.5% | 0.612 |
| (+) | 56 | 80.4% | |
| NSAID user | | | |
| (−) | 177 | 82.5% | |
| (+) | 0 | 96.8% | |
| Underlying diseases | | | |
| (−) | 133 | 84.2% | 0.294 |
| (+) | 44 | 77.5% | |
| Gastroduodenal diseases | | | |
| Gastritis | 102 | 80.8% | 0.693 |
| Peptic ulcer | 75 | 84.0% | |
| Eradication regimen | | | |
| DCA therapy | 90 | 83.3% | 0.736 |
| RCA therapy | 87 | 81.6% | |
| Compliance | | | |
| Good | 173 | 83.2% | 0.142 |
| Poor | 4 | 50.0% | |
| Antibiotic resistance | | | |
| Clarithromycin resistance | | | 0.046* |
| Susceptible | 58 | 93.1% | |
| Resistant | 9 | 66.7% | |
| Amoxicillin | | | |
| Susceptible | 67 | 89.6% | |
| Resistant | 0 | 80.0% | |
| Metronidazole resistance | | | 0.181 |
| Susceptible | 52 | 92.3% | |
| Resistant | 15 | 80.0% | |

* denotes P < 0.05.
confirmed that the presence of clarithromycin was an independent factor predictive of treatment failure (odds ratio: 6.75). Our findings were consistent with several previous studies that demonstrated clarithromycin as a key factor influencing eradication outcome of standard triple therapy.\(^{28–30}\) The prevalence of *H. pylori* strains harboring amoxicillin resistance in Taiwan ranged from 0% to 2.3% in previous reports.\(^{19,20,23,24,31,32}\) In the current trial, the rate of resistant strains to amoxicillin 0%. Since none of the *H. pylori* strains were resistant to amoxicillin, assessing the impact of amoxicillin resistance on eradication outcome of standard triple therapy was precluded. It merits further studies to investigate whether amoxicillin resistance is another independent factor predicting treatment failure of the therapy.

This study was an open-label, noninferior, randomized controlled trial. We recruited 197 patients for the study assuming 8% of eradication difference and 10% loss of follow-up. The statistic power and type 1 error of this analysis were 90% and 5%, respectively. The strengths of this study included providing the data regarding antibiotic resistance. Additionally, this study investigated the impacts of antibiotic resistances on eradication rate of standard triple therapy. However, the study has several limitations. First, the current study was conducted only in a single country. The results should therefore be confirmed in other countries with different patterns of antibiotic resistances. Second, antibiotic susceptibility data were only available in some of the patients because most of the patients were referred from other gastroenterologists and culture was not performed at initial endoscopy. Additionally, the genetic factors of hosts such as *CYP2C19* genotypes determining eradication were not examined in this study. Nonetheless, this study is the pilot study to investigate the eradication rate of dexlansoprazole MR-based triple therapy. In addition, the study confirms that dexlansoprazole MR- and conventional PPI-based triple therapies have comparable eradication rates for *H. pylori* infection.

In conclusion, our study demonstrates that dexlansoprazole MR-based triple therapy can achieve a similar eradication rate as rabeprazole-based therapy. Since the cost of the single-dose dexlansoprazole MR (60 mg) regimen is lower than that of the double-dose rabeprazole (20 mg) regimen, single-dose dexlansoprazole-based triple therapy can reasonably be recommended for the first-line eradication of *H. pylori*.

**ACKNOWLEDGMENTS**

The authors are indebted to study nurses L.Y. Wang and Y.S. Chen for their assistance.

**REFERENCES**

1. Suerbaum S, Michetti P. Helicobacter pylori infection. *N Engl J Med*. 2002;347:1175–1186.

2. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet*. 2009;374:1449–1461.

3. Graham DY, Lew GM, Klein PD, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized controlled study. *Ann Intern Med*. 1992;116:705–708.

4. Sung JY, Chung SCS, Ling TKW, et al. Antibacterial treatment of gastric ulcer associated with Helicobacter pylori. *N Engl J Med*. 1995;332:139–142.

5. Zucca E, Dreyling M. ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol*. 2009;20(suppl 4):113–114.

6. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2009;24:1587–1600.

7. Asaka M, Kato M, Takahashi S, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter*. 2010;15:1–20.

8. Suerbaum S, Leyein H, Klemm K, et al. Antibacterial activity of pantoprazole and omeprazole against *Helicobacter pylori*. *Eur J Clin Microbiol Infect Dis*. 1991;19:134–143.

9. Hassan DJ, Stark RM, Greenman J, et al. Activities of beta-lactams and macrolides against *Helicobacter pylori*. *Antimicrob Agents Chemother*. 1999;43:1387–1392.

10. Katsuki H, Yagi H, Arimori K, et al. Determination of R (+)- and S (-)-lansoprazole using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans. *Pharm Res*. 1996;13:611–615.

11. Fass R, Chey WD, Zakko ZF, et al. Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. *Aliment Pharmacol Ther*. 2009;29:1261–1272.

12. Vakily M, Zhang W, Wu J, et al. Pharmacokinetics and pharmacodynamics of a known active PPI with a novel Dual Delayed Release technology, dexlansoprazole MR: a combined analysis of randomized controlled clinical trials. *Curr Med Res Opin*. 2009;25:627–638.

13. Metz DC, Howden CW, Perez MC, et al. Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. *Aliment Pharmacol Ther*. 2009;29:742–754.

14. Peura DA, Pimer B, Hunt B, et al. Distinguishing the impact of dexlansoprazole on heartburn vs. regurgitation in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2013;38:1303–1311.

15. Howden CW, Larsen LM, Perez MC, et al. Clinical trial: efficacy and safety of dexlansoprazole MR 60 and 90 mg in healed erosive oesophagitis—maintenance of healing and symptom relief. *Aliment Pharmacol Ther*. 2009;30:895–907.

16. Hsu PI, Lai KH, Lin CK, et al. A prospective randomized trial of esomeprazole versus pantoprazole-based triple therapy for *Helicobacter pylori* eradication. *Am J Gastroenterol*. 2005;100:2387–2392.

17. Miner P, Katz PO, Chen Y, et al. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol*. 2003;98:2616–2620.

18. Kukulka M, Eisenberg C, Nudurupati S. Comparator pH study to evaluate the single-dose pharmacodynamics of dual delayed-release dexlansoprazole 60 mg and delayed-release esomeprazole 40 mg. *Clin Exp Gastroenterol*. 2011;4:213–220.
19. Hsu PI, Lai KH, Wu CJ, et al. High-dose versus low-dose esomeprazole-based triple therapy for *Helicobacter pylori* infection. *Eur J Clin Invest*. 2007;7:724–730.

20. Hsu PI, Wu DC, Chen WC, et al. Comparison of 7-day triple, 10-day sequential and 7-day concomitant therapies for *Helicobacter pylori* infection: a randomized controlled trial. *Antimicrob Agents Chemother*. 2014;214:5936–5942.

21. Hsu PI, Lai KH, Hsu PN, et al. Helicobacter pylori infection and the risk of gastric malignancy. *Am J Gastroenterol*. 2007;102:1–6.

22. Wu DC, Hsu PI, Tseng HH, et al. Helicobacter pylori infection: a randomized, controlled study comparing 2 rescue therapies after failure of standard triple therapies. *Medicine*. 2011;90:180–185.

23. Hsu PI, Wu DC, Wu JY, et al. Is there a benefit to extending the duration of *Helicobacter pylori* sequential therapy to 14 days? *Helicobacter*. 2011;16:146–152.

24. Hsu PI, Wu DC, Wu JY, et al. Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter*. 2011;16:139–145.

25. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut*. 2010;59:1143–1153.

26. Chuah SK, Tsay FW, Hsu PI, et al. A new look at anti-*Helicobacter pylori* therapy. *World J Gastroenterol*. 2011;17:3971–3975.

27. Serrano D, Torrado S, Torrado-Santiago S, et al. The influence of CYP2C19 genetic polymorphism on the pharmacokinetics/pharmacodynamics of proton pump inhibitor-containing *Helicobacter pylori* treatments. *Curr Drug Metab*. 2012;13:1303–1312.

28. Megraud F. *H. pylori* antibiotic resistance: prevalence, importance, and advances in testing. *Gut*. 2004;53:1374–1384.

29. Luther J, Higgins PD, Schoenfeld PS, et al. Empiric quadruple vs triple therapy for primary treatment of *Helicobacter pylori* infection: systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol*. 2010;105:65–73.

30. De Francesco V, Margiotta M, Zullo A, et al. Clarithromycin-resistant genotypes and eradication of *Helicobacter pylori*. *Ann Intern Med*. 2006;144:v94–100.

31. Yang JC, Lin CJ, Wang HL, et al. High dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. *Clin Gastroenterol Hepatol*. 2015;13:895–905.

32. Liou JM, Chang CY, Chen MJ, et al. The primary resistance of *Helicobacter pylori* in Taiwan after the National Policy to Restrict Antibiotic Consumption and Its Relation to Virulence Factors: a nationwide study. *PLoS One*. 2015;10:e0124199.