World Journal of Clinical Cases

Submit a Manuscript: http://www.f6publishing.com

World J Clin Cases 2018 October 26; 6(12): 514-520

DOI: 10.12998/wjcc.v6.i12.514

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Basic Study

CYP2C19 polymorphism has no influence on rabeprazole-based hybrid therapy for *Helicobacter pylori* eradication

Tsung-Jung Lin, Hsi-Chang Lee, Chih-Lin Lin, Chung-Kwe Wang, Kuan-Yang Chen, Deng-Chyang Wu

Tsung-Jung Lin, Department of Health care and Social Work, Taipei University of Marine Technology, New Taipei 25172, Taiwan

Tsung-Jung Lin, Hsi-Chang Lee, Chih-Lin Lin, Chung-Kwe Wang, Kuan-Yang Chen, Department of Gastroenterology, Taipei City Hospital, Taipei 10629, Taiwan

Kuan-Yang Chen, Institute of Clinical Medicine, National Yang-Ming University, Taipei 11221, Taiwan

Kuan-Yang Chen, Institute of Neuroscience, National Chengchi University, Taipei 11651, Taiwan

Deng-Chyang Wu, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 80708, Taiwan

Deng-Chyang Wu, Division of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung 80708, Taiwan

Deng-Chyang Wu, Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung 80708, Taiwan

ORCID number: Tsung-Jung Lin (0000-0001-7739-1001); Hsi-Chang Lee (0000-0003-1151-005X); Chih-Lin Lin (0000-0002-4400-6258); Chung-Kwe Wang (0000-0003-0992-2143); Kuan-Yang Chen (0000-0002-4125-5494); Deng-Chyang Wu (0000-0003-3742-0634).

Author contributions: Lin TJ, designed the study and wrote manuscript; Lin TJ, Lee HC, Lin CL, Wang CK, Chen KY, collected data; Wu DC, offered the idea of this study and helped in literature review; Lin TJ, Chen KY designed and supervised the study and statistical analysis.

Institutional review board statement: This study was carried out according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board and ethics committee of Taipei City Hospital (TCHIRB-1011111).

Conflict-of-interest statement: The authors declare no conflict of interest relevant to this study. The article had been published as a poster in the meeting of Asia Pacific Digestive Week 2015 in Taiwan.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Kuan-Yang Chen, MD, Attending Doctor, Department of Gastroenterology, Taipei City Hospital, 11F., No. 10, Sec. 4, Renai Rd., Da-an District, Taipei 10629, Taiwan. daa13@tpech.gov.tw
Telephone: +886-2-27093600-1159
Fax: +886-2-27047859

Received: June 9, 2018
Peer-review started: June 9, 2018
First decision: July 3, 2018
Revised: August 8, 2018
Accepted: August 30, 2018
Article in press: August 30, 2018
Published online: October 26, 2018

Abstract

AIM

To evaluate the impact of cytochrome P450 2C19 (CYP2C19) and interleukin-1β (IL-1β) polymorphisms on the efficacy of *Helicobacter pylori* (*H. pylori*) eradication by using rabeprazole-based hybrid therapy.

METHODS

A total of 88 *H. pylori*-infected patients were recruited to receive 14-d of hybrid therapy from March 2013 to May 2014. Three patients were excluded from analysis because of incomplete compliance. Either a follow-up endoscopy or ^{13}C-urea test was performed to determine the results of *H. pylori* eradication therapy. The genotypes of CYP2C19 and IL-1β were analyzed to investigate the impact on treatment effect.

RESULTS

The total eradication rate of *H. pylori* was 92.94% (79/85). According to the CYP2C19 genotypes, the rates of *H. pylori* eradication were 89.19% in extensive metabolizers (EM) and 95.83% in non-EM. The *H. pylori* eradication rates regarding the IL-1β genotypes were 92.59% in the normal acid secretion group and 93.10% in the low acid secretion group. After multivariable logistic regression analysis, both the genotypes of CYP2C19 and IL-1β had no significant influences on the eradication rates of *H. pylori*.

CONCLUSION

The CYP2C19 and IL-1β polymorphisms are not significantly independent factors of *H. pylori* eradication using rabeprazole-based hybrid therapy.

Key words: *Helicobacter pylori*; Cytochrome P450 2C19; Interleukin-1β; Hybrid therapy; Rabeprazole

Core tip: In this study, we investigated the efficacy of hybrid therapy as a first-line treatment for *Helicobacter pylori* eradication and evaluated the independent predictor associated with eradication efficacy, including cytochrome P450 2C19, interleukin-1β (IL-1β)-511 polymorphism and antibiotic resistance. This study is pilot work investigating the impact of the IL-1β-511 polymorphism on the eradication rate of hybrid therapy.

Lin TJ, Lee HC, Lin CL, Wang CK, Chen KY, Wu DC. CYP2C19 polymorphism has no influence on rabeprazole-based hybrid therapy for *Helicobacter pylori* eradication. *World J Clin Cases* 2018; 6(12): 514-520 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i12/514.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i12.514

INTRODUCTION

The global infection rate of *Helicobacter pylori (H. pylori)* is more than 50%. The infection of *H. pylori* is associated with gastric cancer, gastric ulcer, duodenal ulcer, non-ulcer dyspepsia, chronic gastritis, and mucosa-associated lymphoid tissue lymphoma[1-4]. The efficacy of standard proton pump inhibitor (PPI)-clarithromycin-amoxicillin triple therapy for *H. pylori* eradication has decreased to an unacceptable level (< 80%) due to rising rates of antibiotic resistance in most countries, especially clarithromycin[4-7]. Therefore, several novel first-line regimens have been proposed, including sequential, concomitant and hybrid therapies.

The hybrid therapy, first proposed by Hsu *et al*[8], is an effective treatment method, and a 14-d hybrid therapy can achieve a > 95% eradication rate of *H. pylori* in their study. Hybrid therapy is composed of PPI and amoxicillin for 14 d, and clarithromycin and metronidazole/tinidazole for the final 7 d. This is similar to the hybrid form of the sequential (the first 7 d) and concomitant therapies (the last 7 d). Two recent reports of systematic review and meta-analysis showed that hybrid therapy can achieve similar eradication rates of *H. pylori* compared with sequential or concomitant therapies[9,10].

The PPI is metabolized by the hepatic cytochrome P450 system, especially CYP2C19[11]. Three different genotypes of CYP2C19, including extensive metabolizers (EM), intermediate metabolizers and poor metabolizers (PM), will have different degrees of PPI metabolism. The PM genotype will result in higher intragastric pH levels and higher effectiveness in *H. pylori* eradication due to the low pH level of the stomach that may affect the stabilization of acid-labile antibiotics, such as clarithromycin[12]. Therefore, the EM genotype of CYP2C 19 may result in treatment failure for *H. pylori* eradication[13]. Since rabeprazole is mainly metabolized by a non-enzymatic reaction[14], the CYP2C19 polymorphism may have less influence on the efficacy of rabeprazole-based *H. pylori* eradication treatment[15].

The interleukin (IL)-1 family of cytokines comprises 11 members, including seven pro-inflammatory agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ) and four defined or putative antagonists [IL-1R antagonist (IL-1Ra), IL-36Ra, IL-37, and IL-38] that exert anti-inflammatory activities[16]. The proinflammatory cytokine IL-1β is a strong inhibitor of gastric acid secretion and is highly expressed in the gastric mucosa of *H. pylori*-infected patients[17]. Different genotypes of IL-1β have been reported to have different influences on gastric acid secretion[18]. The IL-1β-511 C/T or T/T genotype has low gastric acid secretion and the IL-1β-511 C/C genotype has normal gastric acid secretion. Therefore, the efficacy of *H. pylori* eradication may be affected by the particular IL-1β-511 genetic polymorphism. One study reported that CYP2C19 genotype-dependent differences in eradication rates of one-week triple therapy were only observed in patients with the IL-1β-511 C/C type[19].

In the initial study of hybrid therapy, no significant factors related to treatment failure were found; however, the CYP2C19 polymorphism was not analyzed[8]. The one study addressing the influence of CYP2C19 by using hybrid therapy as a first-line treatment for *H. pylori* eradication found that resistance to clarithromycin or metronidazole and poor compliance were the independent factors of treatment failure[20]. Thus, the CYP2C19 polymorphism was not the significant predictor.

The goals of our study were to investigate the efficacy of hybrid therapy as a first-line treatment for *H. pylori* eradication and to evaluate the independent predictor associated with eradication efficacy, including CYP2C19, IL-1β-511 polymorphisms and antibiotic resistance. This study is pilot work investigating the impact of IL-1β-511 polymorphisms on the eradication rate of hybrid therapy.

MATERIALS AND METHODS

Patients

At the out-patient Department of Gastroenterology in Taipei City Hospital, Ren-Ai Branch, patients without a history of *H. pylori* eradication were recruited consecutively from March 2013 to May 2014. All of the patients received endoscopic examinations, and biopsies of the gastric mucosa was evaluated by rapid urease test, histology and tissue cultures. The infection of *H. pylori* was defined as either (1) a positive result of culture; or (2) positive results of both the rapid urease test and histological examination. The following patients were excluded: (1) previously treated for *H. pylori* infection; (2) use of antibiotics within the preceding 30 d; (3) regular use of a PPI (> 3 times per week) in the 30 d before enrollment; (4) allergy to any medication in this study; (5) known to interact with study medication; (6) use of concomitant antibiotics; (7) previous surgery of the stomach; (8) presence of Zollinger–Ellison syndrome; (9) presence of a serious medical condition; and (10) pregnancy or lactation. The study was approved by the Institutional Review Board and ethics committee of Taipei City Hospital (TCHIRB-1011111). Written informed consents were provided by all participants.

Interventions

A total 88 patients with *H. pylori* infections were included in our study and treated with 14 d of hybrid therapy (20 mg rabeprazole and 1000 mg amoxicillin twice daily for 7 d, followed by 20 mg rabeprazole, 1000 mg amoxicillin, 500 mg clarithromycin and 500 mg metronidazole twice daily for 7 d). A written handout with instructions about how to take the drugs correctly was given to the patients. Medical history and demographic data were obtained by a well-trained interviewer who interviewed the patients by using a standardized questionnaire. Patients were arranged to return to evaluate the drug compliance and adverse events 2 wk after the start of drug administration. Endoscopic examination with biopsy for histology, rapid urease test, and culture was repeated to assess the status of *H. pylori* infection 8 wk after the completion of *H. pylori* eradication. If the patient refused an endoscopy during follow-up, the ^{13}C-urea test was alternatively used at least 4 wk after the completion of therapy. *H. pylori* eradication was defined as (1) a negative result of the ^{13}C-urea test; or (2) negative results of both the rapid urease test and histological examination.

Questionnaires

The questionnaires contained questions regarding personal medical histories and demographic data, including systemic disease, age, gender, alcohol, smoking, tea and coffee consumption. Drinkers were defined as drinking more than one cup of alcoholic beverage per day, and smokers were defined as consuming more than one pack of cigarettes per week. The adverse events included bitter taste, headache, dizziness, nausea, vomiting, anorexia, abdominal pain, diarrhea, constipation, fatigue and skin rash.

Diagnosis of H. pylori infection

Rapid urease test: The results of the rapid urease test (Delta West Bently, Western, Australia) were interpreted as positive if the color of the gel turned pink or red six hours after examination at room temperature.

Histological examination and culture: We performed biopsies from the lesser curvature site of the antrum and corpus of gastric mucosa for histological examination. The biopsy specimens were smeared on the surface of a Columbia blood agar plate and then incubated at 35℃ under microaerobic conditions for 5 d. When a curvy, gram-negative bacterium was found on the smear, the Gram stain was defined as a positive result. The pathologists were blinded to the results of the laboratory or genotypic tests as well as to the therapies each patient received. If one or more colonies of Gram-negative bacilli with positive urease, oxidase, and catalase tests were found, the result of the *H. pylori* culture was defined as positive.

^{13}C-urea test: Seventy-five mg ^{13}C-Urea mixed with 100 mL of fresh water was used as the test drink. The ^{13}C-urea was manufactured by the Institute of *Wagner Analysen Technik Vertriebs GmbH,* Germany.

Analysis of CYP2C19 and IL-1β-511 genotypes

Peripheral blood was drawn in an EDTA vacutainer, and a commercially available kit (Qiagen K.K., Tokyo, Japan) was used to isolate DNA from the leukocytes. The method of polymerase chain reaction–restriction fragment length polymorphism established by de Morais *et al*[21,22] with minor modifications was performed to analyze the wild-type (wt) gene and the two mutated alleles, CYP2C19 m1 and CYP2C19 m2[21-23]. Homozygous EM (*i.e.*, wild-type) was defined as wt/wt; heterozygous EM as wt/m1 and wt/m2; and PM as m1/m1, m2/m2 and m1/m2, respectively. We also used the method of polymerase chain reaction–restriction fragment length polymorphism with allele-specific primers to identify the C-to-T single nucleotide polymorphism of IL-1β-511[24].

Analysis of antibiotics resistance

To culture *H. pylori*, we rubbed one antral gastric biopsy specimen on the surface of a Campy-BAP agar plate

Table 1 Univariable analysis of the clinical factors and genotyped polymorphisms *n* (%)

Variable	Eradication (*n* = 79)	No eradication (*n* = 6)	*P* value
Age (yr)	51.95 ± 13.48	53.17 ± 12.06	0.831
Sex (male:female)	35:44	2:4	0.693
Smoking	14 (17.72)	0 (0)	0.583
Alcohol	19 (24.05)	1 (16.67)	1.000
Betel	1 (1.27)	0 (0)	1.000
Coffee	56 (70.89)	4 (66.67)	1.000
Tea	59 (74.68)	4 (66.67)	0.646
NSAID user	7 (8.86)	1 (16.67)	0.458
Steroid user	3 (3.80)	0 (0)	1.000
Anticoagulant user	4 (5.06)	1 (16.67)	0.316
CYP2C19 genotype			0.380
HomoEM	33 (41.77)	4 (66.67)	
HeteroEM	36 (45.57)	1 (16.67)	
PM	10 (12.66)	1 (16.67)	
IL-1β-511 genotype			0.934
CC	25 (31.65)	2 (33.33)	
CT	32 (40.51)	2 (33.33)	
TT	22 (27.85)	2 (33.33)	
Resistance (*n* = 65)	(*n* = 61)	(*n* = 4)	
Amoxicillin	0/61 (0)	0/4 (0)	
Clarithromycin	8/61 (13.11)	0/4 (0)	1.000
Metronidazole	25/61 (40.98)	1/4 (25.00)	0.644

Data are expressed as mean ± SD or *n* (%). NSAID: Non-steroid anti-inflammatory drug; CYP2C19: Cytochrome P450 2C19; EM: Extensive metabolizer; PM: Poor metabolizer; IL-1β: Interleukin-1β.

(Brucella agar, Difco, Sparks Maryland) + IsoVitalex (Gibco, Grand Island, New York) + 10% whole sheep blood. The agar plate then was incubated at 37 ℃ under microaerobic conditions (5%O_2, 10% CO_2 and 85%N_2) for 4-5 d. Antibiotic susceptibility for the *H. pylori* strain was tested for clarithromycin, metronidazole and amoxicillin by using an E-test (AB Biodisck, Solna, Sweden). Resistance to clarithromycin, metronidazole, and amoxicillin was defined as a minimal inhibitory concentration value of 1 μg/mL, 8 μg/mL, and 0.5 μg/mL, respectively.

Statistical analysis

Data were summarized as mean ± SD. Data were compared between groups on the basis of *H. pylori* eradication results. Categorical variables were compared with the chi-square test or Fisher's exact test as required. Continuous variables were compared between groups by using the unpaired *t*-test. The Mann-Whitney test was used when appropriate. Multivariable logistic regression analysis was used to identify the independent predictors related to the eradication of *H. pylori*. A *P* value < 0.05 was statistically significant.

RESULTS

Baseline demographic data of patients

A total of 88 *H. pylori*-infected patients were treated with hybrid therapy. Three patients were excluded from analysis because of poor compliance. According to the treatment outcome, baseline demographic data from the 85 patients with complete therapy of *H. pylori* eradication are shown in Table 1. A total of 79 patients had successful eradication of *H. pylori* and the eradication rate was 92.94% using 14-d of hybrid therapy.

Genotypes of CYP2C19 and single nucleotide polymorphisms of the IL-1β gene (SNP-511)

Three different patterns of CYP2C19 polymorphisms were analyzed in our study, including homozygous EMs, heterozygous EMs and PMs. The prevalence of CYP2C19 homEM, hetEM, PM was 41.77%, 45.57%, 12.66% in patients with eradicated *H. pylori* and 66.67%, 16.67%, 16.67% in patients without eradicated *H. pylori*, respectively. In addition, three different allelic patterns of the IL-1β-511 gene were examined, including C/C, C/T, and T/T. The CC/CT/TT genotype frequency was 31.65%, 40.51%, 27.85% in patients with eradicated *H. pylori* and 33.33%, 33.33%, 33.33% in patients without eradicated *H. pylori*, respectively (Table 1).

Factors associated with H. pylori eradication

No significant clinical or genetic factors were found to be associated with successful eradication of *H. pylori* by univariable analysis, including age, gender, coffee/tea drinking, alcohol drinking, betel using, use of steroid, anticoagulant or non-steroid anti-inflammatory drug, antibiotic resistance, or CYP2C19 and IL-1β-511 polymorphisms (Table 1). The rates of *H. pylori* eradication were 89.19% in EM and 95.83% in non-EM (Table 2). Patients were classified into two groups according to IL-1B-511 genetic polymorphisms. The normal acid secretion group was defined as those with the alleles (C/C), and the low acid secretion group was defined as those with either the alleles (T/T) or (C/T). The cure rates of each IL-1β-511 genetic polymorphism in relation to

Table 2 Eradication rates according to cytochrome P450 2C19 and interleukin-1β genotypes *n* (%)

Hybrid therapy	(*n* = 85)	IL-1β-511 C/C (normal gastric acid) (*n* = 27)	IL-1β-511 C/T, T/T (low gastric acid) (*n* = 58)
	79/85 (92.94)	25/27 (92.59)	54/58 (93.10)
CYP2C19 EM (*n* = 37)	33/37 (89.19)	13/14 (92.86)	20/23 (86.96)
CYP2C19 PM and hetero EM (*n* = 48)	46/48 (95.83)	12/13 (92.31)	34/35 (97.14)
P value	0.649	1.000	0.556

CYP2C19: Cytochrome P450 2C19; IL-1β: Interleukin-1β; EM: Extensive metabolizer; PM: Poor metabolizer.

Table 3 Multivariable logistic regression analysis of independent predictors of *Helicobacter pylori* eradication rates

Variable	Odds ratio	95%CI	*P* value
EM *vs* PM and hetero EM	0.359	0.062–2.075	0.252
IL-1β-511 C/C *vs* IL-1β-511 C/T, T/T	1.047	0.175–6.251	0.960

EM: Extensive metabolizer; PM: Poor metabolizer; IL-1β: Interleukin-1β.

the CYP2C19 genotype are showed in Table 2. The rates of *H. pylori* eradication were 92.59% in the normal acid secretion group and 93.10% in the low acid secretion group. There was no statistically significant difference in the eradication rates of *H. pylori* between the two CYP2C19 genotype subgroups (EM and non-EM) for both normal acid (IL-1β-511 C/C) and low acid (IL-1β-511 C/T and T/T) secretion groups. After multivariable analysis, both CYP2C19 and IL-1β-511 genetic polymorphisms were not significant factors of *H. pylori* eradication by using 14-d of hybrid therapy (Table 3).

DISCUSSION

The failure of *H. pylori* eradication is mainly related to antibiotic resistance, poor compliance of patients, and duration of therapy[25]. The present study was performed to investigate the eradication rate of *H. pylori* by using 14-d of hybrid therapy. In addition, the main purpose of our study was to further explore the influence of CYP2C19 and IL-1β-511 genotypes on the outcome of hybrid therapy. Therefore, patients with poor compliance were excluded from analysis.

In one review article, a total of 1871 patients in 12 studies received hybrid therapy[26]. The eradication rate of *H. pylori* was 82.6%-99.1%, and pooled analysis showed the eradication rate was 91.2% in per-protocol analyses. The other review article with meta-analysis included 2516 patients from eight studies, and the mean cure rate of hybrid therapy was 93.3% (*n* = 1109, range: 85.7%-99.1%) by per-protocol analyses[27]. Our study found that the eradication rate was 92.94% by using 14-d of hybrid therapy, which was comparable to the results of the two review articles. Nonetheless, one study in the population with high antibiotic resistance rates found that the eradication rate of hybrid therapy was 86.0% in per-protocol analyses and graded as an unacceptable level[20]. In addition, the study showed that resistance to clarithromycin, resistance to metronidazole and poor compliance were the significant predictors of treatment failure for hybrid therapy and that the CYP2C19 genotype was not. In our study, no independent factors were found to be associated with treatment failure. The first key factor was compliance; however, we excluded patients with poor compliance from the beginning. Secondarily, because hybrid therapy achieved a high eradication rate in our study, the number of patients with treatment failure was too small to identify the significant predictors. Two other studies also explored the influence of antibiotic resistance on the treatment outcome of hybrid therapy[8,28]. Both of the studies had not demonstrated the significance of antibiotic resistance on the eradication rate of *H. pylori.* This may be related to the lack of antimicrobial susceptibility of *H. pylori* for most patients included in the studies. The study revealed that a compliance of more than 80% was the only significant factor of successful eradication[28]. However, the first study of 14-d hybrid therapy found that no risk factors, including compliance, influenced the efficacy of *H. pylori* eradication[8]. Another study of 10-d hybrid therapy also showed that no clinical factors were associated with treatment failure, however antibiotic resistance and CYP2C19 genotype were not investigated in the study[29].

The key finding of our study was that CYP2C19 and IL-1β-511 genotypes had no influence on the treatment outcome of 14-d hybrid therapy. To date, only one study had examined the influence of the CYP2C19 genotype on hybrid therapy[20]. This study showed no significant effect of CYP2C19 polymorphisms on the eradication rate of *H. pylori*. In one study of 12-d reverse hybrid

therapy, the CYP2C19 genotype also had no significant impact on the treatment outcome[30]. The limitation of our study was that the number of patients may be too small to identify the significant factors predicting eradication failure.

Both CYP2C19 and IL-1β polymorphisms had no significant impact on rabeprazole-based hybrid therapy. Our findings suggest that rabeprazole may be used as a priority in EMs of CYP2C19 to maintain the eradication rate of *H. pylori*.

ARTICLE HIGHLIGHTS

Research background

In the initial study of hybrid therapy, no significant factors related to treatment failure were found; however, the cytochrome P450 2C19 (CYP2C19) polymorphism was not analyzed. Only one study addressed the influence of CYP2C19 by using hybrid therapy as a first-line treatment for *Helicobacter pylori* (*H. pylori*) eradication.

Research objectives

The aims of this study were to investigate the efficacy of hybrid therapy as a first-line treatment for *H. pylori* eradication, and to evaluate the independent predictors associated with eradication efficacy, including CYP2C19, the interleukin (IL)-1β-511 polymorphism, and antibiotic resistance.

Research methods

About 88 *H. pylori*-infected patients were recruited to receive 14-d of hybrid therapy. Endoscopies or ^{13}C-urea tests were performed to determine the results of *H. pylori* eradication therapy. To investigate the impact on treatment effect, the genotypes of CYP2C19 and IL-1β were analyzed.

Research results

The total eradication rate of *H. pylori* was 92.94%. The rates of *H. pylori* eradiation were 89.19% in extensive metabolizers (EM) and 95.83% in non-EM, according to the CYP2C19 genotypes. Both the genotypes of CYP2C19 and IL-1β had no significant influence on the eradication rates of *H. pylori*.

Research conclusions

The CYP2C19 and IL-1β polymorphisms are not significantly independent factors on rabeprazole-based hybrid therapy for *H. pylori* eradication.

Research perspectives

The limitation of this study was that the number of patients may be too small to identify the significant factors predicting eradication failure. In addition, the findings suggest that rabeprazole may be used as a priority in EMs of CYP2C19 to maintain the eradication rate of *H. pylori*.

REFERENCES

1 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]

2 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]

3 **Alakkari A**, Zullo A, O'Connor HJ. Helicobacter pylori and non-malignant diseases. *Helicobacter* 2011; **16** Suppl 1: 33-37 [PMID: 21896083 DOI: 10.1111/j.1523-5378.2011.00878.x]

4 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ; European Helicobacter Study Group. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

5 **Graham DY**, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143-1153 [PMID: 20525969 DOI: 10.1136/gut.2009.192757]

6 **Megraud F**, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Glupczynski Y; Study Group participants. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; **62**: 34-42 [PMID: 22580412 DOI: 10.1136/gutjnl-2012-302254]

7 **Song Z**, Zhang J, He L, Chen M, Hou X, Li Z, Zhou L. Prospective multi-region study on primary antibiotic resistance of Helicobacter pylori strains isolated from Chinese patients. *Dig Liver Dis* 2014; **46**: 1077-1081 [PMID: 25220697 DOI: 10.1016/j.dld.2014.08.038]

8 **Hsu PI**, Wu DC, Wu JY, Graham DY. 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 [PMID: 21435092 DOI: 10.1111/j.1523-5378.2011.00828.x]

9 **Song ZQ**, Zhou LY. Hybrid, sequential and concomitant therapies for Helicobacter pylori eradication: A systematic review and meta-analysis. *World J Gastroenterol* 2016; **22**: 4766-4775 [PMID: 27217708 DOI: 10.3748/wjg.v22.i19.4766]

10 **He L**, Deng T, Luo H. Meta-analysis of sequential, concomitant and hybrid therapy for Helicobacter pylori eradication. *Intern Med* 2015; **54**: 703-710 [PMID: 25832929 DOI: 10.2169/internalmedicine.54.3442]

11 **Furuta T**, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 2005; **20**: 153-167 [PMID: 15988117 DOI: 10.2133/dmpk.20.153]

12 **Kita T**, Tanigawara Y, Aoyama N, Hohda T, Saijoh Y, Komada F, Sakaeda T, Okumura K, Sakai T, Kasuga M. CYP2C19 genotype related effect of omeprazole on intragastric pH and antimicrobial stability. *Pharm Res* 2001; **18**: 615-621 [PMID: 11465416 DOI: 10.1023/A:1011025125163]

13 **Sugimoto M**, Furuta T. Efficacy of tailored Helicobacter pylori eradication therapy based on antibiotic susceptibility and CYP2C19 genotype. *World J Gastroenterol* 2014; **20**: 6400-6411 [PMID: 24914361 DOI: 10.3748/wjg.v20.i21.6400]

14 **Ishizaki T**, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. *Aliment Pharmacol Ther* 1999; **13** Suppl 3: 27-36 [PMID: 10491726 DOI: 10.1046/j.1365-2036.1999.00022.x]

15 **Fock KM**, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, Lam SK, Xiao SD, Tan HJ, Wu CY, Jung HC, Hoang BH, Kachintorn U, Goh KL, Chiba T, Rani AA; Second Asia-Pacific Conference. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. *J Gastroenterol Hepatol* 2009; **24**: 1587-1600 [PMID: 19788600 DOI: 10.1111/j.1440-1746.2009.05982.x]

16 **Palomo J**, Dietrich D, Martin P, Palmer G, Gabay C. The interleukin (IL)-1 cytokine family--Balance between agonists and antagonists in inflammatory diseases. *Cytokine* 2015; **76**: 25-37 [PMID: 26185894 DOI: 10.1016/j.cyto.2015.06.017]

17 **Jung HC**, Kim JM, Song IS, Kim CY. Helicobacter pylori induces an array of pro-inflammatory cytokines in human gastric epithelial cells: quantification of mRNA for interleukin-8, -1 alpha/beta, granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein-1 and tumour necrosis factor-alpha. *J Gastroenterol Hepatol* 1997; **12**: 473-480 [PMID: 9257236 DOI: 10.1111/j.1440-1746.1997.tb00469.x]

18 **El-Omar EM**, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, Rothman N, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; **404**: 398-402 [PMID: 10746728 DOI: 10.1038/35006081]

19 **Take S**, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Inaba T, Yamamoto K, Okada H, Yokota K, Oguma K, Shiratori Y. Interleukin-1beta genetic polymorphism influences the effect of cy-

tochrome P 2C19 genotype on the cure rate of 1-week triple therapy for Helicobacter pylori infection. *Am J Gastroenterol* 2003; **98**: 2403-2408 [PMID: 14638340 DOI: 10.1111/j.1572-0241.2003.07707.x]

20 **Song Z**, Zhou L, Zhang J, He L, Bai P, Xue Y. Hybrid Therapy as First-Line Regimen for Helicobacter pylori Eradication in Populations with High Antibiotic Resistance Rates. *Helicobacter* 2016; **21**: 382-388 [PMID: 26809022 DOI: 10.1111/hel.12294]

21 **De Morais SM**, Wilkinson GR, Blaisdell J, Meyer UA, Nakamura K, Goldstein JA. Identification of a new genetic defect responsible for the polymorphism of (S)-mephenytoin metabolism in Japanese. *Mol Pharmacol* 1994; **46**: 594-598 [PMID: 7969038]

22 **de Morais SM**, Wilkinson GR, Blaisdell J, Nakamura K, Meyer UA, Goldstein JA. The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. *J Biol Chem* 1994; **269**: 15419-15422 [PMID: 8195181]

23 **Kubota T**, Chiba K, Ishizaki T. Genotyping of S-mephenytoin 4'-hydroxylation in an extended Japanese population. *Clin Pharmacol Ther* 1996; **60**: 661-666 [PMID: 8988068 DOI: 10.1016/S0009-9236(96)90214-3]

24 **Kato S**, Onda M, Yamada S, Matsuda N, Tokunaga A, Matsukura N. Association of the interleukin-1 beta genetic polymorphism and gastric cancer risk in Japanese. *J Gastroenterol* 2001; **36**: 696-699 [PMID: 11686480 DOI: 10.1007/s005350170033]

25 **Kanizaj TF**, Kunac N. Helicobacter pylori: future perspectives in therapy reflecting three decades of experience. *World J Gastroenterol* 2014; **20**: 699-705 [PMID: 24574743 DOI: 10.3748/wjg.v20.i3.699]

26 **Song ZQ**, Liu J, Zhou LY. Hybrid Therapy Regimen for Helicobacter Pylori Eradication. *Chin Med J* (Engl) 2016; **129**: 992-999 [PMID: 27064046 DOI: 10.4103/0366-6999.179803]

27 **Hsu PI**, Lin PC, Graham DY. Hybrid therapy for Helicobacter pylori infection: A systemic review and meta-analysis. *World J Gastroenterol* 2015; **21**: 12954-12962 [PMID: 26668516 DOI: 10.3748/wjg.v21.i45.12954]

28 **Molina-Infante J**, Romano M, Fernandez-Bermejo M, Federico A, Gravina AG, Pozzati L, Garcia-Abadia E, Vinagre-Rodriguez G, Martinez-Alcala 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]

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

30 **Hsu PI**, Kao SS, Wu DC, Chen WC, Peng NJ, Yu HC, Wang HM, Lai KH, Cheng JS, Chen A, Chuah SK, Tsay FW; Taiwan Acid-Related Disease Study Group. A Randomized Controlled Study Comparing Reverse Hybrid Therapy and Standard Triple Therapy for Helicobacter pylori Infection. *Medicine* (Baltimore) 2015; **94**: e2104 [PMID: 26632893 DOI: 10.1097/MD.0000000000002104]

P- Reviewer: Chiurillo MA, Hsu PI, Slomiany BL
S- Editor: Wang JL **L- Editor**: Filipodia **E- Editor**: Tan WW

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com