J Antimicrob Chemother 2016; **71**: 2280–2285
doi:10.1093/jac/dkw118 Advance Access publication 21 April 2016

Journal of Antimicrobial Chemotherapy

Antibiotic resistance and CYP2C19 polymorphisms affect the efficacy of concomitant therapies for *Helicobacter pylori* infection: an open-label, randomized, single-centre clinical trial

Junbo Hong[1]†, Xu Shu[1]†, Dongsheng Liu[2], Yin Zhu[1], Chuan Xie[2], Yong Xie[2], Kunhe Zhang[2], Anjiang Wang[1], Huifang Xiong[1], Huilie Zeng[3], Huiqiang Yu[3], Jiuhong Ma[4], Youxiang Chen[4], Xuan Zhu[1] and Nonghua Lu[1]*

[1]Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, 17 Yongwai Zheng Street, Nanchang, Jiangxi, P.R. China; [2]Institute of Digestion, The First Affiliated Hospital of Nanchang University, 17 Yongwai Zheng Street, Nanchang, Jiangxi, P.R. China; [3]Department of Statistics of Medical College of Nanchang University, 681 Bayi Road, Nanchang, Jiangxi, P.R. China; [4]Digestive Endoscopy Center, The First Affiliated Hospital of Nanchang University, 17 Yongwai Zheng Street, Nanchang, Jiangxi, P.R. China

*Corresponding author. E-mail: lunonghua10359@126.com
†The first two authors contributed equally to this work.

Received 2 January 2016; returned 29 January 2016; revised 4 March 2016; accepted 9 March 2016

Objectives: We evaluate the efficacy of concomitant therapy for *Helicobacter pylori* infection and the associated factors that influence it in China, where it has not previously been investigated.

Methods: In this prospective study, 374 consecutive patients with *H. pylori* infection were randomly assigned to 10 day regimens of concomitant therapy with different proton pump inhibitors: esomeprazole (20 mg)/omeprazole (20 mg), amoxicillin (1000 mg), clarithromycin (500 mg) and metronidazole (400 mg). All drugs were administered twice daily. A [^{13}C]urea breath test was performed at least 4 weeks after the completion of treatment. Gene polymorphisms and antimicrobial susceptibility were determined.

Results: A total of 374 patients with active, uncomplicated duodenal ulcer disease were enrolled in the study (187 cases in each group). The overall eradication rate resulting from concomitant therapy was 90.7% (PP) and 86.1% (ITT) and the eradication rate was significantly higher in the group that received an esomeprazole-based regimen compared with the group that received an omeprazole-based regimen [95.4% versus 86.0%, respectively, $P=0.003$ (PP) and 89.8% versus 82.4%, $P=0.036$ (ITT), respectively]. Moreover, the omeprazole-based regimen was an independent risk factor for treatment failure ($P=0.039$), as were CYP2C19 extensive metabolizer ($P=0.005$), clarithromycin ($P=0.000$) and metronidazole resistance ($P=0.000$). In addition, CYP2C19 polymorphisms and antibiotic resistance had a synergistic effect on eradication rates. The majority of side effects were mild and none was serious.

Conclusions: The 10 day concomitant therapy yielded an eradication rate of nearly 90%. Antibiotic resistance, CYP2C19 polymorphisms and their interactions were closely associated with regimen efficacy.

Introduction

Helicobacter pylori is closely associated with gastritis, peptic ulcer disease, gastric cancer and various extra-gastric diseases.[1] Recently, the eradication rate resulting from standard triple therapy has steadily declined to far below 80%,[2,3] mainly due to clarithromycin resistance.[1] Triple therapy is therefore no longer recommended for *H. pylori* eradication in China.[4]

Non-bismuth quadruple therapies have been recommended to address antibiotic resistance.[1] Sequential therapy becomes ineffective in the presence of metronidazole resistance and has been shown to be inferior (eradication rates <80%) to standard triple therapy in China.[4,5] Concomitant therapies consisting of a proton pump inhibitor (PPI), amoxicillin, clarithromycin and metronidazole have the advantage of being effective in the presence of isolated clarithromycin or metronidazole resistance; indeed, it is only overcome by the presence of dual clarithromycin and metronidazole resistance.[6,7] However, few studies have evaluated the efficacy and safety of concomitant therapies in China, especially in strains with antimicrobial resistance.

The cytochrome P450 isoenzyme 2C19 (CYP2C19) and IL-1β polymorphisms, which affect the availability of administered PPI and intragastric acidity, are factors that may influence eradication regimens.[1] For example, the efficacy of administering an omeprazole-based triple therapy at a standard dose depends upon the CYP2C19 genotype status, which is less likely to affect the efficacy of esomeprazole-based regimens.[8,9] Moreover, the eradication rate among patients with IL-1β-511 C/C is significantly

lower than the rate in patients with IL-1β-511 C/T and T/T.[10] However, inconsistent results have been reported concerning the roles they play in eradication regimens,[11,12] and their effects have not been verified in concomitant therapies.

In this study, we evaluated the effectiveness of a 10 day concomitant therapy with two PPIs (esomeprazole and omeprazole) in patients with uncomplicated duodenal ulcer disease (DU) in the active phase and infected with *H. pylori*.

Methods

Trial design and participants

See Methods S1 (available as Supplementary data at *JAC* Online).

Eradication and rescue regimens

The patients were randomly (1:1, computer-generated sequence and sealed opaque envelopes) assigned to receive different 10 day concomitant therapies consisting of esomeprazole (20 mg)/omeprazole (20 mg), amoxicillin (1000 mg), clarithromycin (500 mg) and metronidazole (400 mg). All drugs were taken concurrently twice daily. If *H. pylori* eradication failed, the patients were offered an empirical bismuth-containing quadruple regimen consisting of esomeprazole (20 mg), bismuth potassium citrate (220 mg), amoxicillin (1000 mg) and furazolidone (100 mg). All drugs were taken concurrently twice daily for 10 days.

Outcome evaluation

The primary outcomes were as follows: (i) the *H. pylori* eradication rate of the concomitant therapy; and (ii) the effect of antibiotic resistance and CYP2C19 polymorphisms on eradication. The secondary outcomes were the safety of the regimen and other influencing factors.

Demographics, side effects and compliance evaluation

See Methods S2.

Evaluation of H. pylori resistance and eradication

See Methods S3.

Detection of CYP2C19 and IL-1β polymorphisms

See Methods S4.

Statistical analysis

See Methods S5.

Ethics

See Methods S6.

Results

Patient screening

A total of 586 uncomplicated DU patients were screened. Of these patients, 212 were excluded. A final total of 374 DU patients (227 males and 147 females with a mean age ± SD of 40.2 ± 11.8 years) were included in the study (187 patients in each group). A total of 13 patients (3.5%) withdrew (Figure S1).

Demographics, side effects and compliance

See Results S1, Tables S1 and S2.

Antimicrobial susceptibility

See Results S2 and Table S3.

Prevalence of CYP2C19 and IL-1β polymorphisms

See Results S3 and Table S1.

Eradication of H. pylori infection

The eradication rates resulting from the concomitant therapy were 90.7% and 86.1% based on PP and ITT analyses, respectively. The esomeprazole-based regimen yielded a higher eradication rate than the omeprazole-based regimen in both PP and ITT analyses (95.4% versus 86.0%, OR = 3.388, 95% CI = 1.477–7.772, $\chi^2 = 9.128$, $P = 0.003$; 89.8% versus 82.4%, OR = 1.895, 95% CI = 1.034–3.471, $\chi^2 = 4.378$, $P = 0.036$) (Table S4). Furthermore, the omeprazole-based regimen was an independent predictor of treatment failure (OR = 2.573, 95% CI = 1.050–6.305, $\chi^2 = 4.274$, $P = 0.039$) (Table S5).

Effect of antibiotic resistance on eradication rates

The eradication rates for the clarithromycin- and metronidazole-susceptible strains were significantly higher than the rates for the clarithromycin- and metronidazole-resistant strains (91.0% versus 55.8%, OR = 8.013, 95% CI = 4.112–15.615, $\chi^2 = 46.405$, $P = 0.000$; 94.2% versus 80.3%, OR = 4.013, 95% CI = 1.894–8.506, $\chi^2 = 14.794$, $P = 0.000$). Moreover, clarithromycin (OR = 19.451, 95% CI = 7.050–53.668, $\chi^2 = 32.849$, $P = 0.000$) and metronidazole (OR = 12.592, 95% CI = 3.671–43.189, $\chi^2 = 16.225$, $P = 0.000$) resistances were independent risk factors for treatment failure in the multivariate analysis (Table S5).

The eradication rate was highest for the dual clarithromycin- and metronidazole-susceptible strains (95.6%), followed by the single metronidazole-resistant (87.6%) and clarithromycin-resistant (84.2%) strains. The rates for all of these strains were significantly higher than the rate for the dual-resistant strain (39.4%) ($P = 0.003$–0.000). However, the eradication rates for the single clarithromycin- and metronidazole-resistant strains were not significantly lower than the rate for the dual susceptible strain (84.2% versus 95.6%, OR = 0.244, 95% CI = 0.056–1.073, $\chi^2 = 3.996$, $P = 0.046$; 87.6% versus 95.6%, OR = 0.013, 95% CI = 0.128–0.816, $\chi^2 = 6.229$, $P = 0.013$; Bonferroni correction, $P < 0.008$) (Table S6).

Effect of CYP2C19 and IL-1β polymorphisms on eradication rates

The eradication rate among patients with CYP2C19 extensive metabolizer (EM) was significantly lower than the rate among patients with intermediate metabolizer + poor metabolizer (IM + PM) (80.6% versus 90.0%, OR = 0.465, 95% CI = 0.257–0.843, $\chi^2 = 6.571$, $P = 0.01$). Moreover, CYP2C19 EM was an independent predictor of treatment failure (OR = 0.291, 95% CI = 0.124–0.684, $\chi^2 = 8.014$, $P = 0.005$) (Table S5). There was no difference in the eradication rate between EM and IM + PM in the esomeprazole

group (89.2% versus 90.3%, OR=0.890, 95% CI=0.340–2.328, χ^2=0.057, P=0.812). However, the eradication rate for IM+PM was significantly higher than the rate for EM in the omeprazole group (89.6% versus 72.8%, OR=3.220, 95% CI=1.457–7.119, χ^2=8.899, P=0.003). The eradication rate for EM was significantly higher in the esomeprazole group than in the omeprazole group (89.2% versus 72.8%, OR=3.076, 95% CI=1.273–7.432, χ^2=6.623, P=0.01). However, there was no difference in the eradication rate for IM+PM between the groups (90.3% versus 89.6%, OR=1.074, 95% CI=0.445–2.592, χ^2=0.025, P=0.874) (Table S7).

No association was found between IL-1β polymorphisms and eradication rates (Table S5).

Synergistic effect of CYP2C19 polymorphisms and antibiotic resistance on eradication rates

The eradication rate was highest in patients with CYP2C19 IM+PM/clarithromycin susceptibility/metronidazole susceptibility (96.3%) and lowest in patients with CYP2C19 EM/clarithromycin resistance/metronidazole resistance (72.7%). In addition, the eradication rate was significantly higher in patients with CYP2C19 IM+PM/clarithromycin resistance/metronidazole resistance than in patients with CYP2C19 EM/clarithromycin resistance/metronidazole resistance (86.2% versus 72.7%, OR=2.349, 95% CI=1.219–4.525, χ^2=6.721, P=0.01), but no difference was found between patients with CYP2C19 EM/clarithromycin susceptibility/metronidazole susceptibility and CYP2C19 IM+PM/clarithromycin susceptibility/metronidazole susceptibility (94.6% versus 96.3%, OR=0.679, 95% CI=0.132–3.496, χ^2=0.216, P=0.688). In patients with both CYP2C19 EM/clarithromycin susceptibility/metronidazole susceptibility and CYP2C19 IM+PM/clarithromycin susceptibility/metronidazole susceptibility, the eradication rate was significantly higher than the rate in patients with CYP2C19 EM/clarithromycin resistance/metronidazole resistance (94.6% versus 72.7%, OR=6.625, 95% CI=1.909–22.995, χ^2=11.006, P=0.001 and 96.3% versus 72.7%, OR=9.75, 95% CI=2.835–33.526, χ^2=17.818, P=0.000, respectively). Moreover, the eradication rate was significantly higher in patients with CYP2C19 IM+PM/clarithromycin susceptibility/metronidazole susceptibility than in patients with CYP2C19 IM+PM/clarithromycin resistance/metronidazole resistance (96.3% versus 86.2%, OR=4.151, 95% CI=1.189–14.499, χ^2=5.721, P=0.019). However, there was no difference in the eradication rate between patients with CYP2C19 EM/clarithromycin susceptibility/metronidazole susceptibility and CYP2C19 IM+PM/clarithromycin resistance/metronidazole resistance (94.6% versus 86.2%, OR=0.355, 95% CI=0.101–1.250, χ^2=2.803, P=0.133) (Table S8).

Other factors that influenced eradication rates

See Results S4 and Table S5.

Rescue therapies

See Results S5.

Discussion

In the present study, we evaluated the effect of antibiotic resistance and CYP2C19 polymorphisms on concomitant therapy with two PPIs. Our results confirm that 10 day concomitant therapy is an effective, safe and well-tolerated treatment option. Antibiotic resistance, CYP2C19 EM and a compliance rate <80% were independent predictors of treatment failure. CYP2C19 polymorphisms and antibiotic resistance had a synergistic effect on eradication rates. Dual resistance, but not single resistance, was associated with treatment failure.

As previously mentioned, antibiotic resistance has progressively increased and varies substantially in China. The overall resistance rates for metronidazole, clarithromycin and amoxicillin are reported to be 67.2%–95.4%, 21.5%–37.5% and 0.1%–6.8%, respectively.[13,14] Concomitant therapy has been widely recommended in many areas to address antibiotic resistance[1] and 10 day regimens result in superior eradication rate (>90%) in some areas.[15–17] However, the efficacy of these regimens varies substantially between areas, likely because of differences in patterns of antibiotic resistance.[15,18,19] Moreover, sufficient data on the eradication rates of concomitant therapies in mainland China are not available. A recent study indicated unsatisfactory eradication rates of 78.3% (ITT) and 87.4% (PP) at three tertiary hospitals, in which the clarithromycin resistance rate was 48.8%.[20] However, in the present study, a 10 day concomitant therapy yielded effective eradication rates of 86.1% (ITT) and 90.7% (PP), with a clarithromycin resistance rate of 13.9%, indicating that this approach may represent a promising regimen in areas with relatively low clarithromycin resistance.

Antibiotic resistance was closely associated with the efficacy of the regimen.[1] One initial study verified that the eradication rate was highest in patients with dual metronidazole- and clarithromycin-susceptible strains, followed by single metronidazole- or clarithromycin-resistant strains, and lowest in dual-resistant strains.[20] Moreover, single metronidazole or clarithromycin resistance, but not dual resistance, could be overcome by concomitant therapy, as mentioned in some previous studies.[6,7] In this study, clarithromycin and metronidazole resistances were independent predictors of treatment failure. The eradication rate was significantly higher in cases with dual susceptibility (clarithromycin and metronidazole) and single-resistant strains than in cases with dual resistance. Moreover, dual resistance, but not single resistance, was closely associated with treatment failure. These results demonstrate a synergistic effect of antibiotics in this regimen, although dual antibiotic resistance may compromise its effectiveness.

PPIs, which elevate gastric pH to increase the susceptibility of *H. pylori* to antibiotics, are the primary components of eradication regimens.[21] Esomeprazole showed a better pharmacokinetic profile than omeprazole in the CYP2C19 (*S*-mephenytoin 4′-hydroxylase) genotype, with increased systemic exposure and less interindividual variability.[22] A previous study revealed that esomeprazole, when administered once daily at a standard dose, provided more effective control of gastric acid at the steady state than standard doses of omeprazole.[23] Esomeprazole-based triple therapy was effective in *H. pylori* eradication and was superior to an omeprazole-based regimen in a meta-analysis.[24,25] However, one initial study revealed that the efficacies of esomeprazole- and omeprazole-based regimens were comparable,[26] indicating that the inconsistent outcomes in tests of the efficacy of the two PPIs remained an issue. Moreover, the efficacy of the two PPIs in concomitant therapy had not previously been examined. In this study, we show that use of an esomeprazole-based regimen results in a higher eradication rate than use of an omeprazole-based regimen.

Plasma PPI levels and intragastric pH during PPI treatment are influenced by CYP2C19 polymorphisms.[27] Treatment with omeprazole at a standard dosage did not effectively maintain acid inhibition for a full 24 h, especially in patients with CYP2C19 EM.[28] However, in CYP2C19 EM patients, twice-daily administration of 20 mg of esomeprazole resulted in stronger inhibition of gastric acid than that observed with omeprazole.[29] The influence of CYP2C19 on eradication rates has recently been described in several studies and it was found to be a potentially independent predictor of the efficacy of triple therapy.[30,31] However, because outcomes have been inconsistent, no association has been demonstrated between CYP2C19 and eradication rates.[11,32,33] Moreover, the roles of CYP2C19 polymorphisms in concomitant therapy have not been well defined. In the present study, we reveal that the eradication rate was significantly lower in patients with CYP2C19 EM than in patients with CYP2C19 IM+PM, especially in patients who received the omeprazole-based regimen. In contrast, the efficacy of the esomeprazole-based regimen is not affected by CYP2C19 polymorphisms. These results reveal that the eradication rate that resulted from administration of the concomitant therapy was affected by CYP2C19 polymorphisms in the omeprazole group but not in the esomeprazole group.

One initial study reported that the eradication rate was significantly lower in patients with IL-1β-511 C/C than in patients with IL-1β-511 C/T and T/T.[10] However, IL-1β polymorphisms were not found to be an independent risk factor of treatment outcomes in a different study.[12] In the present study, we found that IL-1β polymorphisms were not associated with the efficacy of the therapy. These results indicate that the effect of IL-1β polymorphisms on concomitant therapy remains unclear.[1]

The organism, gastric environment, host and drug regimens often have inter-related roles in treatment failure.[2] The activities of clarithromycin and amoxicillin and the survival of *H. pylori* vary depending on the gastric pH,[21] which is affected by CYP2C19 polymorphisms during PPI treatment.[27] However, no report has shown an interaction between CYP2C19 polymorphisms and antibiotic resistance in patients undergoing concomitant therapy. In our study, the eradication rate was highest among patients with CYP2C19 IM+PM who were infected with dual-susceptible strains and lowest in patients with CYP2C19 EM infected with dual-resistant strains, indicating a synergistic effect between CYP2C19 polymorphisms and antibiotic resistance. These results show that *H. pylori* therapy should be tailored based on these influential factors.[34]

As previously mentioned, drug compliance is considered one of the predominant factors that affects treatment outcomes.[1] In one study, it was the only clinical factor that was found to influence the treatment efficacy of concomitant therapy.[35] The present study also showed that the eradication rate achieved with concomitant therapy was significantly lower in patients with a compliance rate $<80\%$ than in patients with a compliance rate $\geq 80\%$. These results clearly demonstrate that compliance is a determinant for eradication and that eradication rates can be increased by improving compliance.

A larger number of mild side effects have been reported by patients undergoing concomitant therapy compared with those undergoing standard triple therapy because of the addition of metronidazole.[36] Moreover, the prevalence of side effects varies in different studies.[35,37] In our study, the overall rate of side effects was 40.5%, although the reported side effects were mostly mild and were always relieved without treatment.

There are some limitations to this study. The efficacies of concomitant therapies with different durations (e.g. 10 versus 14 days) and PPI doses (e.g. standard versus high doses) were not investigated. In addition, the efficacy of the regimen may have been compromised due to the low doses of metronidazole (400 mg, twice daily) applied in the study. However, the *H. pylori* eradication rate remained relatively constant as the dose of metronidazole increased (high dose: 800 mg, twice daily; medium dose: 400 mg, three-times daily; and low dose: 400 mg, twice daily) when it was administered with omeprazole and amoxicillin.[38] The standard culture method used for *H. pylori* was the agar dilution method. A previous study showed that if the Etest MIC results for metronidazole yield values between 8 and 32 mg/L, the MIC should be re-evaluated using another method.[39]

In summary, the 10 day concomitant therapy yielded an effective eradication rate (nearly 90%). We expect this approach to be a promising regimen for eradicating *H. pylori* infection in highly antibiotic-resistant areas. An omeprazole-based regimen (initiated due to CYP2C19 polymorphisms), antibiotic resistance and a compliance rate $<80\%$ were independent predictors of treatment failure. Moreover, antibiotic resistance had a synergistic effect with CYP2C19 EM on the efficacy of the regimen. Multicentre studies using different PPI durations and regimen doses are needed to verify the efficacy of this concomitant therapy in Chinese subjects.

Acknowledgements

We are grateful to all of the endoscopists and nurses who provided technical expertise and assistance during this study.

Funding

This study was supported by a grant from the Jiangxi Provincial Department of Science and Technology (No. 20113BCB24019).

Transparency declarations

We purchased a Developmental Editing package from American Journal Experts (Durham, USA).

Author contributions

J. H., X. S. and N. L., study concept and design; J. H., acquisition of data; J. H., X. S., Y. X., K. Z. and A. W., analysis and interpretation of data; J. H., drafted the manuscript; J. H., A. W. and N. L., critical revision; J. H., H. Z. and H. Y., statistical analysis; J. H., D. L., Y. Z., C. X., Y. X., K. Z., A. W., H. X., J. M., Y. C., X. Z. and N. L., administrative, technical or material support; J. H., Y. Z., J. M. and N. L., study supervision; J. H., X. S., D. L., Y. Z., C. X., Y. X., K. Z., A. W., H. X., H. Z., H. Y., J. M., Y. C., X. Z. and N. L., approved final version of manuscript.

Supplementary data

Methods S1 to S6, Figure S1, Results S1 to S5 and Tables S1 to S8 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Malfertheiner P, Megraud F, O'Morain CA *et al*. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence consensus report. *Gut* 2012; **61**: 646–64.

2 Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143–53.

3 Malfertheiner P, Bazzoli F, Delchier J *et al*. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet* 2011; **377**: 905–13.

4 Zhou L, Zhang J, Chen M *et al*. A comparative study of sequential therapy and standard triple therapy for *Helicobacter pylori* infection: a randomized multicenter trial. *Am J Gastroenterol* 2014; **109**: 535–41.

5 Xie C, Lu N. Review: clinical management of *Helicobacter pylori* infection in China. *Helicobacter* 2015; **20**: 1–10.

6 Ang TL, Fock KM, Song M *et al*. Ten-day triple therapy versus sequential therapy versus concomitant therapy as first-line treatment for *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2015; **30**: 1134–9.

7 Georgopoulos SD, Xirouchakis E, Martinez-Gonzalez B *et al*. Clinical evaluation of a ten-day regimen with esomeprazole, metronidazole, amoxicillin, and clarithromycin for the eradication of *Helicobacter pylori* in a high clarithromycin resistance area. *Helicobacter* 2013; **18**: 459–67.

8 Zhao F, Wang J, Yang Y *et al*. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Helicobacter* 2008; **13**: 532–41.

9 Hunfeld NG, Touw DJ, Mathot RA *et al*. A comparison of the acid-inhibitory effects of esomeprazole and rabeprazole in relation to pharmacokinetics and CYP2C19 polymorphism. *Aliment Pharmacol Ther* 2012; **35**: 810–8.

10 Sugimoto M, Furuta T, Yamaoka Y. Influence of inflammatory cytokine polymorphisms on eradication rates of *Helicobacter pylori*. *J Gastroenterol Hepatol* 2009; **24**: 1725–32.

11 Kuo C, Hsu P, Kuo F *et al*. Comparison of 10 day bismuth quadruple therapy with high-dose metronidazole or levofloxacin for second-line *Helicobacter pylori* therapy: a randomized controlled trial. *J Antimicrob Chemother* 2013; **68**: 222–8.

12 Take S, Mizuno M, Ishiki K *et al*. Interleukin-1beta genetic polymorphism influences the effect of cytochrome P 2C19 genotype on the cure rate of 1-week triple therapy for *Helicobacter pylori* infection. *Am J Gastroenterol* 2003; **98**: 2403–8.

13 Su P, Li Y, Li H *et al*. Antibiotic resistance of *Helicobacter pylori* isolated in the southeast coastal region of China. *Helicobacter* 2013; **18**: 274–9.

14 Song Z, Zhang J, He L *et al*. Prospective multi-region study on primary antibiotic resistance of *Helicobacter pylori* strains isolated from Chinese patients. *Dig Liver Dis* 2014; **46**: 1077–81.

15 Kongchayanun C, Vilaichone R, Pornthisarn B *et al*. Pilot studies to identify the optimum duration of concomitant *Helicobacter pylori* eradication therapy in Thailand. *Helicobacter* 2012; **17**: 282–5.

16 Cuadrado-Lavín A, Salcines-Caviedes JR, Diaz-Perez A *et al*. 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**: 2376–81.

17 Wu D, Hsu P, Wu J *et al*. Sequential and concomitant therapy with four drugs is equally effective for eradication of *H. pylori infection*. *Clin Gastroenterol Hepatol* 2010; **8**: 36–41.e1.

18 McNicholl AG, Marin AC, Molina-Infante J *et al*. Randomised clinical trial comparing sequential and concomitant therapies for *Helicobacter pylori* eradication in routine clinical practice. *Gut* 2014; **63**: 244–9.

19 Greenberg ER, Anderson GL, Morgan DR *et al*. 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. *Lancet* 2011; **378**: 507–14.

20 Zhou L, Zhang J, Song Z *et al*. Tailored versus triple plus bismuth or concomitant therapy as initial *Helicobacter pylori* treatment: a randomized trial. *Helicobacter* 2016; **21**: 91–9.

21 Scott D, Weeks D, Melchers K *et al*. The life and death of *Helicobacter pylori*. *Gut* 1998; **43** Suppl 1: S56–60.

22 Sugimoto M, Furuta T. Efficacy of esomeprazole in treating acid-related diseases in Japanese populations. *Clin Exp Gastroenterol* 2012; **5**: 49–59.

23 Miner P Jr, 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**: 2616–20.

24 Tulassay Z, Stolte M, Sjölund M *et al*. Effect of esomeprazole triple therapy on eradication rates of *Helicobacter pylori*, gastric ulcer healing and prevention of relapse in gastric ulcer patients. *Eur J Gastroenterol Hepatol* 2008; **20**: 526–36.

25 McNicholl AG, Linares PM, Nyssen OP *et al*. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2012; **36**: 414–25.

26 Subei IM, Cardona HJ, Bachelet E *et al*. One week of esomeprazole triple therapy vs. 1 week of omeprazole triple therapy plus 3 weeks of omeprazole for duodenal ulcer healding in *Helicobacter pylori*-positive patients. *Dig Dis Sci* 2007; **52**: 1505–12.

27 Furuta T, Shirai N, Sugimoto M *et al*. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 2005; **20**: 153–67.

28 Sugimoto M, Shirai N, Nishino M *et al*. Comparison of acid inhibition with standard dosages of proton pump inhibitors in relation to CYP2C19 genotype in Japanese. *Eur J Clin Pharmacol* 2014; **70**: 1073–8.

29 Sahara S, Sugimoto M, Uotani T *et al*. Twice-daily dosing of esomeprazole effectively inhibits acid secretion in CYP2C19 rapid metabolisers compared with twice-daily omeprazole, rabeprazole or lansoprazole. *Aliment Pharmacol Ther* 2013; **38**: 1129–37.

30 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**: 1303–12.

31 Gawrońska-Szklarz B, Wrześniewska J, Starzyńska T *et al*. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with *Helicobacter pylori* infection. *Eur J Clin Pharmacol* 2005; **61**: 375–9.

32 Lee VWY, Chau TS, Chan AKW *et al*. Pharmacogenetics of esomeprazole or rabeprazole-based triple therapy in *Helicobacter pylori* eradication in Hong Kong non-ulcer dyspepsia Chinese subjects. *J Clin Pharm Ther* 2010; **35**: 343–50.

33 Liou J, Chen C, Chen M *et al*. Empirical modified sequential therapy containing levofloxacin and high-dose esomeprazole in second-line therapy for *Helicobacter pylori* infection: a multicentre clinical trial. *J Antimicrob Chemother* 2011; **66**: 1847–52.

34 Sugimoto M, Uotani T, Sahara S *et al*. Efficacy of tailored *Helicobacter pylori* eradication treatment based on clarithromycin susceptibility and maintenance of acid secretion. *Helicobacter* 2014; **19**: 312–8.

35 Molina-Infante J, Romano M, Fernandez-Bermejo M *et al*. Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter*

pylori infection in populations with high rates of antibiotic resistance. *Gastroenterology* 2013; **145**: 121–8.e1.

36 Molina-Infante J, Lucendo AJ, Angueira T *et al*. Optimised empiric triple and concomitant therapy for *Helicobacter pylori* eradication in clinical practice: the OPTRICON study. *Aliment Pharmacol Ther* 2015; **41**: 581–9.

37 Kao SS, Chen WC, Hsu PI *et al*. 7-Day nonbismuth-containing concomitant therapy achieves a high eradication rate for *Helicobacter pylori* in Taiwan. *Gastroenterol Res Pract* 2012; **2012**: 463985.

38 Bardhan KD, Bayerdörffer E, Veldhuyzen Van Zanten SJO *et al*. The HOMER Study: the effect of increasing the dose of metronidazole when given with omeprazole and amoxicillin to cure *Helicobacter pylori* infection. *Helicobacter* 2000; **5**: 196–201.

39 Hachem CY, Clarridge JE, Reddy R *et al*. Antimicrobial susceptibility testing of *Helicobacter pylori*. Comparison of E-test, broth microdilution, and disk diffusion for ampicillin, clarithromycin, and metronidazole. *Diagn Microbiol Infect Dis* 1996; **24**: 37–41.