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Research Article

Effects of the EM CYP2C19 type and *MDR1 3435CC* gene on *Helicobacter pylori* eradication rate in patients with duodenal ulcer by the four-drug regimen of rabeprazole, bismuth, tetracycline, and tinidazole

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Abstract

Background: The *MDR1* genotype and the CYP2C19 phenotype determine how much PPI is absorbed from the gut and how much is processed in the liver.

Objective: To assess the impact of *CYP2C19* and *MDR1 C3435T* gene polymorphisms on the efficiency of *H. pylori* eradication treatment with a 4-drug regimen of rabeprazole, bismuth, tetracycline, and tinidazole (RBTT) in patients with duodenal ulcers.

Methods: The study was conducted at Can Tho University of Medicine and Pharmacy. Gene polymorphisms for *CYP2C19* and *MDR1 C3435T* were detected through a blood test. The RBTT 4-drug regimen was used to eradicate *H. pylori*.

Results: The success rate of the RBTT regimen for eradicating *H. pylori* in female patients with the CYP2C19 EM phenotype + *MDR1 3435CC* genotype was 20.0% lower than the rate of 91.7% for the group without both phenotype and genotype (p = 0.01, OR = 0.02, 95%CI: 0.00–0.45).

Conclusion: Compared to the group lacking both phenotypes and genotypes, female patients with the CYP2C19 EM phenotype + *MDR1 3435CC* genotype had a lower rate of *H. pylori* eradication by RBTT regimen.

Keywords

Helicobacter pylori, CYP2C19, *MDR1 C3435T*

Introduction

Upper gastrointestinal conditions such as peptic ulcer disease, gastric cancer, and duodenal ulcer were associated with *Helicobacter pylori* (*H. pylori*) infection (Graham 2014).

33% of *H. pylori* in Vietnam were resistant to clarithromycin (Binh et al. 2013). The Maastricht IV consensus advised treating *H. pylori* for the first time with a four-drug regimen comprising bismuth in regions where *H. pylori* strains were resistant to clarithromycin in more than 15–20% of cases (Malfertheiner et al. 2012). According to the Vietnam Gastroenterology Association's advice, a 4-drug regimen containing bismuth (PPI, bismuth, tetracycline, metronidazole, or tinidazole) should be used for 7–14 days as the first treatment for *H. pylori* eradication in the South of Vietnam (Vietnam Association of Gastroenterology 2013). Antibiotics, bismuth, and proton pump inhibitors (PPIs) were among the medications used to treat *H. pylori* (Malfertheiner et al. 2007). A variety of factors, such as *CYP2C19* genotype, *MDR1 3435CC* patient genotype, antibiotic resistance of the *H. pylori* bacteria, etc., affected the outcome of *H. pylori* treatment (Sugimoto et al. 2014).

The nitroimidazole class of antibiotics included the drugs metronidazole and tinidazole. On the other hand, Tinidazole might have certain benefits over metronidazole, according to some studies. When cultivating *H. pylori* bacteria and creating antibiograms, metronidazole and clarithromycin were less sensitive to *H. pylori* bacteria than tinidazole and clarithromycin (Svensson et al. 2002). A three-drug regimen comprising metronidazole was less effective than one using tinidazole for treating *H. pylori* eradication (Abbas et al. 2003). In contrast to the three-drug regimen containing metronidazole, which had 3/91 patients experience side effects that necessitated stopping therapy, all 80 patients who received the three-drug regimen containing tinidazole finished the course of treatment (Berutti et al. 2008). With the regimen of ranitidine bismuth citrates, tetracycline, and tinidazole, the results of the second *H. pylori* eradication treatment reached 80% (Rinaldi et al. 1999).

Orally administered PPIs were absorbed through the gastrointestinal mucosa by the membrane transport enzyme P-glycoprotein encoded by the gene *MDR1* (Hoffmeyer et al. 2000; Pauli-Magnus et al. 2001). The *MDR1* gene had 28 exons, the study by Hoffmeyer S. indicated that the expression and function of the *MDR1* gene were correlated with the polymorphism in exon 26 (*C3435T*). The amount of *MDR1* gene expression was 2-fold lower in homozygous T allele carriers than in homozygous C allele carriers (Hoffmeyer et al. 2000). The liver was placed that PPIs were metabolized by the S-mephenytoin hydroxylase enzyme, which was encoded by the *CYP2C19* gene. (Litalien et al. 2005). According to the degree of metabolism, the phenotype of CYP2C19 consisted of fast metabolizer: EM (extensive metabolizer), genotype CYP2C19*1/*1, intermediate metabolizer: IM (intermediate metabolizer), genotype CYP2C19*1/*2, and poor metabolizer: PM (poor metabolizer), genotype CYP2C19*2/*2, *2/*3, and *3/*3 (Maev et al. 2014). The PPI medication rabeprazole was metabolized by the CYP2C19 enzyme the least (Rouby et al. 2018). According to various research conducted throughout the globe, the genotype *MDR1 C3435T* had an impact on how well PPIs including omeprazole, lansoprazole, pantoprazole, and esomeprazole worked to eradicate *H. pylori* (Gawronska-Szklarz et al. 2005; Furuta et al. 2007; Li Meng et al. 2017). When utilizing new-generation PPIs (esomeprazole, rabeprazole), the rate of *H. pylori* eradication in patients with the fast-metabolizing *CYP2C19* genotype was greater than that of first-generation PPIs (McNicholl et al. 2012). The rate of effective *H. pylori* eradication in patients taking the PPI medicine rabeprazole was lower in those with the fast-metabolizing CYP2C19 phenotype than in those with the moderate and poor metabolizers (Kuo et al. 2010; Ormeci et al. 2016). However, several trials utilizing rabeprazole or esomeprazole PPIs found no differences in *H. pylori* eradication rates between CYP2C19 phenotypes (Tang et al. 2013).

As a result, we decided to investigate whether the CYP2C19 phenotype and the *MDR1 C3435T* genotype had an impact on the outcomes of the 4-drug regimen with bismuth used to treat *H. pylori* in Vietnamese patients. This regimen consists of rabeprazole, bismuth, tetracycline, and tinidazole (RBTT) and was administered for 14 days.

Materials and methods

Study materials

Patients at the Hospital of Can Tho University of Medicine and Pharmacy who had duodenal ulcers and had *H. pylori* infection from 2015 to 2016.

Selection criteria

The patient was diagnosed with duodenal ulcer (Endoscopy with duodenal ulcer ≥ 5 mm), *H. pylori* infection diagnosis (both rapid urease test and positive histopathology), and non-treatment *H. pylori* before. Patients who were at least 18 years old. All participants gave informed consent to participate in the study.

Exclusion criteria

Exclusion standards for pre-treatment: patients who had undergone gastric bypass surgery before, problems from a duodenal ulcer, including bleeding from the stomach and perforation. Cirrhosis, cancer, and Crohn's disease patients who also had other serious diseases. Women who were breastfeeding and pregnant. In addition to aspirin, the patient was taking non-steroidal anti-inflammatory medicines. The patient had a history of medication allergies to the ones used in the trial.

Patients who deliberately modified their drug regimens or unilaterally utilized medicines for ailments other than those recommended by their doctors were excluded from receiving treatment (such as non-steroidal anti-inflammatory drugs, aspirin, etc.).

Study design

Type of study: intervention progress, longitudinal follow-up.

Study facilities

Olympus GIF 180 gastroduodenal endoscope from Japan. To fix the stomach mucosa biopsy specimen, the vial included 10% neutral formalin. EDTA (ethylenediaminetetraacetic acid) anticoagulant in 5 mL test tubes. Nam Khoa Trading Service Company Limited, Ho Chi Minh City, provided the sample for the fast urease test (NK-Pylori test).

The Applied Biosystem's PCR machine system 9700 and Beckman Coulter's CEQ 8800 sequencers were used to evaluate the *CYP2C19* and *MDR1 C3435T* genes, respectively.

Drugs for treating duodenal ulcers and getting rid of *H. pylori* were from the hospital pharmacy of Can Tho University of Medicine and Pharmacy. Brand name Pariet 20 mg of the Japanese manufacturer Eisai for rabeprazole sodium. Trymo 120 mg, Colloidal Bismuth Subcitrate 120 mg, Raptakos Brett Company, India. Tinidazole 500 mg (brand name Tinidazol 500 mg), Tetracycline Hydrochloride 500 mg (trade name Tetracyclin 500 mg) by Domesco Company, Vietnam.

Implementation steps

1. Patient reception and clinical examination: Smoking according to the US Centers for Disease Control and Prevention (Centers for Disease Control and Prevention 2009). Drinking according to the AUDIT-C (The Alcohol Use Disorders Identification Test Consumption) alcohol used disorder screening questionnaire by Bradley K.A. (Bradley et al. 2007).
2. Gastroduodenal endoscopy: Diagnosis of duodenal ulcer ≥ 5 mm. We performed biopsies of gastric mucosa with 2 pieces in the antrum 3 cm from the pyloric orifice and 2 pieces in the body on the greater curvature. 2 biopsies (1 in corpus, 1 in antrum) for rapid urease test and 2 biopsies (1 in corpus, 1 in antrum) for histopathology to diagnose *H. pylori* infection.
3. Rapid urease test for *Helicobacter pylori* detection: We took two biopsies (1 in corpus, 1 in antrum), and put them in the sample for rapid urease test. The results must be read in 60 minutes. When the reagent transformed from yellow to lotus pink during a rapid urease test, it was positive. If the test sample's color did not change after the aforementioned period, it was deemed negative.
4. Histopathological tests of the gastric mucosa diagnose *Helicobacter pylori*: we took 2 biopsies (1 in corpus, 1 in antrum), placed them in 2 bottles of 10% formol solution, labeled the bottles with the name and code, and sent the bottles to the University Hospital's Anatomy Department. Medicine Can Tho. We detected *H. pylori* infection on Giemsa and Hematoxylin-eosin staining slides and assessed *H. pylori* density according to the new Sydney Categorization System's classification standards, which was based on histopathology, classified as mild, moderate, or severe. (Dixon et al. 1996).
5. *CYP2C19* gene and *MDR1 C3435T* gene test procedure:

   Blood collection: we assisted the patient in going to the laboratory at Can Tho University of Medicine and Pharmacy to get a blood draw, took 5 mL of blood from the rotary vein, placed it in a test tube with the anticoagulant EDTA, spun the test tube, and used a centrifuge to separate the leukocytes, put in test tubes, stored and preserved.

   Allele-specific bidirectional PCR with the Amplification Refractory Mutation System (ARMS) technique for the *CYP2C19* test (Newton et al. 1989): primer pair (Outer-*CYP2C19**2-F: 5'-CTACACATGTACAATAAAAATTTC-CCCATCAAG-3'/Outer-*CYP2C19**2-R: 5'-CT-GCAGAACAGAGCTTTTCCTATCCTGA-3') detected polymorphisms rs4244285 (G681A-*CYP2C19**2), primer pair (Outer-*CYP2C19**2-F: Outer-*CYP2C19**3-F: 5'-ACATTCCCGG-CCTATTTGTCTTTTACTTTGG-3'/Outer-*CYP2C19**3-R: 5'-GAGCTAATGGGCTTAGAAG-CCTGATCT-3') detected polymorphisms rs4986893 (G636A-*CYP2C19**3). We directed gene sequencing of the *MDR1* gene by the *C3435T* SNP rs1045642 (A/C/T) primer sequence (Outer-MRD1-F: 5'-CTTGTATACAGGTAAGGGT-GATTTGGT-3'/Outer-MDR1-R: 5'-GAAACAT-GACAGTTCCTCCAAGGCATAC-3') (Sanger et al. 1975) was used to conduct the test. The experiment was carried out in the Molecular Biology Department, 108 Central Military Hospital.
6. Treatment of duodenal ulcer with *Helicobacter pylori* infection.

   Patients used a 4-drug regimen with bismuth continuously for 14 days: 2 doses of Rabeprazole (Pariet) 20 mg each day/ four times a day; 120 mg of bismuth (Trymo)/ one pill at a time; took one 500 mg pill of tetracycline four times in one dose; took one 500 mg pill of tinidazole two times in one dose.

   Continued treatment with rabeprazole (Pariet) 20 mg, taking 1 tablet, 2 times in 1, continuously for 14 days to repair the duodenal ulcer once the *H. pylori* eradication program is complete.

   Post-treatment follow-up: Four weeks after the RBTT regimen ended, a second follow-up

appointment was planned for each patient (2 weeks after stopping rabeprazole). Rapid urease test, biopsy of the stomach mucosa, and histological detection of *H. pylori* were all performed during endoscopic assessment of ulcers.

7. Assessment of the efficacy of *H. pylori* infection therapy for duodenal ulcers.
   Assessing two issues—the successful eradication of *H. pylori* and the treatment of *H. pylori*-infected duodenal ulcers—would help determine how effective this approach was (negative *H. pylori* on both rapid urease test and histopathology).
   Patients who had not received effective care: Treatment for *H. pylori* eradication failure results in consideration of switching to a new regimen, under the 2013 recommendation of the Vietnam Association of Gastroenterology (Vietnam Association of Gastroenterology 2013).
   Non-scarred ulcers: continued taking PPIs for another 4 weeks.
8. Data processing and analysis.
   We used the computer program SPSS 20.0, all data were processed. The Pearson Chi-Square Test assessed the proportional difference between the two groups. Use the Fisher's Exact Test if the comparison sample size was 5 in more than 20% of the cases; to ascertain the relationship between the independent and dependent variables, we used a logistic regression analysis (LOGRAPH). The test results were rated as statistically significant when $p < 0.05$.

Results

Patients' characteristics in the study

Of the 102 participants in the trial, 22 were qualified for therapy and genetic testing for the *CYP2C19* and *MDR1C3435T* genes. Ten patients who were eligible for inclusion in the study of the efficacy of the RBTT regimen but did not return for a follow-up exam and endoscopic diagnosis of *H. pylori* and 92 re-examination patients who were eligible (Fig. 1).

Of the 102 duodenal ulcer patients who participated in the study, male patients made up 77.5% of the group, while female patients made up 22.5%. Men had a proportion of the *CYP2C19**2 and *3 alleles of 26.6% and 3.8%, respectively, whereas females had a proportion of 19.6% and 4.3%. With $p = 0.33$ and $p = 1.00$, respectively, there was no difference in the proportions of the *2 and *3 alleles in males compared to females. Similar to how there was no difference between males and females in the ratio of CYP2C19 phenotypes (CYP2C19 EM, IM, and PM phenotypes, respectively), 49.4%, 40.5%, and 10.1% (no CYP2C19 PM phenotype). EM and IM for CYP2C19 were 52.2% and 47.8%, respectively, with a p-value of 0.05 (Table 1).

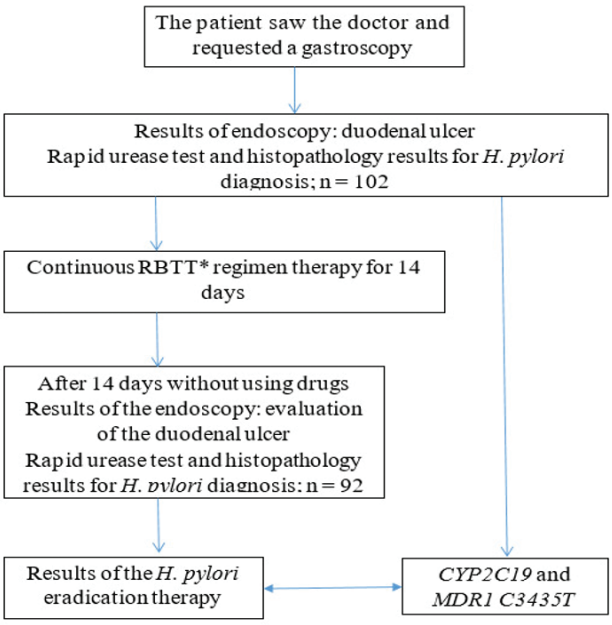

Figure 1. Diagnosis and *H. pylori* eradication therapy. (*) RBTT: rabeprazole, bismuth, tetracycline, tinidazole.

Table 1. The *CYP2C19* allele and phenotypes in 102 individuals with *Helicobacter pylori*-related duodenal ulcers.

CYP2C19 Gene	n	Gender		p	OR, 95% Cl
Allele *2		**Male**	**Female**		
Yes	51	42 (26.6)	9 (19.6)	0.33	1.48,
No	153	116 (73.4)	37 (80.4)		0.66–3.34
Allele *3					
Yes	8	6 (3.8)	2 (4.3)	1	0.86,
No	196	152 (96.2)	44 (95.7)		0.16–4.45
Phenotype of EM					
Yes	51	39 (49.4)	12 (52.2)	0.81	0.89,
No	51	40 (50.6)	11 (47.8)		0.35–2.26
Phenotype of IM					
Yes	43	32 (40.5)	11 (47.8)	0.53	0.74,
No	59	47 (59.5)	12 (52.2)		0.29–1.88
Phenotype of PM					
Yes	8	8 (10.1)	0 (0.0)	-	-
No	94	71 (89.9)	23 (100.0)		

Men and women in the study's 102 *H. pylori* infected duodenal ulcer patients both had *MDR1C3435T* alleles and genotypes. The proportion of the *MDR1 3435T* allele in men was 35.4% lower than that of the *3435T* allele, at 64.6%. The rates of the common *MDR1 C3435T* genotypes were *3435CC* and *3435CT*, accounting for 44.3% and 40.5%, respectively. The *MDR1* genotype *3435CC* accounted for the highest proportion of 60.9%, followed by genotypes *3435CT* and *3435TT* with rates of 34.8% and 21.7%, respectively. In women, *MDR1* allele *3435C* was 78.3% more common than allele *3435T*, at 4.3%. When comparing men and women, there was no difference in the *MDR1 C3435T* genotype and allele ratios ($p > 0.05$) (Table 2).

Among patients with *H. pylori*-infected duodenal ulcers had the CYP2C19 phenotype and the *MDR1 C3435T* genotype, the most common combination is CYP2C19 EM phenotype + *MDR1 3435CC* genotype, which occurred in

25/102 patients, followed by IM + *3435CC* (21/102), IM + *3435CT* (18/102) and EM + *3435CT* (17/102). Other CYP2C19 phenotype + *MDR1 C3435T* genotype were less common. There didn't have *MDR1 3435TT* genotype + CYP2C19 PM phenotype, in particular (Table 3).

Table 2. *MDR1 C3435T* allele and genotype ratio in duodenal ulcer patients infected with *Helicobacter pylori* (n = 102).

Gene *MDR1 C3435T*	n	Gender		p	OR, 95% Cl
Allele *3435T*		**Male**	**Female**		
Yes	66	56 (35.4)	10 (21.7)	0.08	1.97, 0.91–4.28
No	138	102 (64.6)	36 (78.3)		
***3435CC* genotype**					
Yes	49	35 (44.3)	14 (60.9)	0.16	0.51, 0.19–1.31
No	53	44 (55.7)	9 (39.1)		
***3435CT* genotype**					
Yes	40	32 (40.5)	8 (34.8)	0.62	1.27, 0.48–3.36
No	62	47 (59.5)	15 (65.2)		
***3435TT* genotype**					
Yes	13	12 (15.2)	1 (4.3)	0.28	3.94,
No	89	67 (84.8)	22 (95.7)		0.48–32.05

Table 3. Distribution of CYP2C19 phenotypes and *MDR1 C3435T* genotypes in duodenal ulcer patients infected with *Helicobacter pylori*.

CYP2C19 phenotype	*MDR1 C3435T* genotype			Total
	3435CC	*3435CT*	*3435TT*	
EM	25	17	9	**51**
IM	21	18	4	**43**
PM	3	5	0	**8**
Total	**49**	**40**	**13**	**102**

Distribution of *Helicobacter pylori* eradication results according to CYP2C19 phenotype and *MDR1 C3435T* genotype.

After *H. pylori* eradication treatment, 92 patients were examined endoscopically and tested for *H. pylori* bacteria. We found that the rate of successful *H. pylori* eradication in patients with the CYP2C19 EM phenotype was 87.5%, IM was 94.4%, and PM was 100%. There was no difference in *H. pylori* eradication treatment rates between the CYP2C19 EM vs. IM phenotype (p = 0.45) and the CYP2C19 EM vs. IM+PM phenotype (p = 0.27). Results of successful *H. pylori* eradication treatment in genotype *MDR1*: *3435CC* was 87.0%, *3435CT* was 97.1%, and *3435TT* was 90.09%. There was no difference in *H. pylori* eradication treatment rates in *MDR1* genotypes *3435CC* vs. *3435CT* (p = 0.13), *3435CC* vs. *3435TT* (p = 1.00), and *3435CC* vs. *3435CT* + *3435TT* (p = 0.26) (Table 4).

Regarding the factors of CYP2C19 phenotype and *MDR1 C3435T* genotype affecting the efficacy of treatment for eradication of *H. pylori*, we found the *H. pylori* eradication treatment rate in the group of patients with the CYP2C19 EM phenotype and the *MDR1 3435CC* genotype was 80.0%, significantly lower than the rate in the group of patients without both phenotypes and genotypes. However, there was no statistically significant difference between the group without co-factors and the CYP2C19 phenotype (EM + IM) + *MDR1* genotype (*3435CC* + *3435TT*) of 90.4% in terms of the efficiency of *H. pylori* eradication treatment. The times for both phenotype and genotype above were 94.7% (p = 1.00). In the CYP2C19 (EM + IM) phenotype and *MDR1 3435CC* genotype, the *H. pylori* eradication treatment rate was 86.0%, compared with the group without both phenotypes and genotypes at 95.9% (p = 0.14). The eradication rate of *H. pylori* therapy was 87.2% in the CYP2C19 EM phenotype + *MDR1* genotype (*3435CC* + *3435TT*), compared to the group lacking both phenotypes and genotypes at 94.3% (p = 0.27) (Table 5).

Table 4. Results of *Helicobacter pylori* eradication treatment in CYP2C19 phenotype, *MDR1 C3435T* genotype (n = 92).

Factor	n	Eradication		p	OR, 95% Cl
CYP2C19 phenotype		**Success**	**Failure**		
EM	48	42 (87.5)	6 (12.5)	0.45	0.41, 0.07–2.17
IM	36	34 (94.4)	2 (5.6)		
CYP2C19 phenotype					
EM	48	42 (87.5)	6 (12.5)	0.27	0.33, 0.06–1.74
IM + PM	44	42 (95.5)	2 (4.5)		
***MDR1 C3435T* genotype**					
3435CC	46	40 (87.0)	6 (13.0)	0.13	0.19, 0.02–1.71
3435CT	35	34 (97.1)	1 (2.9)		
***MDR1 C3435T* genotype**					
3435CC	46	40 (87.0)	6 (13.0)	1	0.66, 0.07–6.18
3435TT	11	10 (90.9)	1 (9.1)		
***MDR1 C3435T* genotype**					
3435CC	46	40 (87.0)	6 (13.0)	0.26	0.30, 0.05–1.58
3435CT + 3435TT	46	44 (95.7)	2 (4.3)		

Table 5. Results of *Helicobacter pylori* eradication treatment in CYP2C19 phenotype + *MDR1 C3435T* genotype (n = 92).

Factor	n	Eradication		p	OR, 95% Cl
(EM+IM) + (*3435CC* + *3435CT*)		**Success**	**Failure**		
Yes	73	66 (90.4)	7 (9.6)	1	0.52,
No	19	18 (94.7)	1 (5.3)		0.06–4.53
(EM + IM) + *3435CC*					
Yes	43	37 (86.0)	6 (14.0)	0.14	0.26,
No	49	47 (95.9)	2 (4.1)		0.05–1.37
EM + (*3435CC* + *3435CT*)					
Yes	39	34 (87.2)	5 (12.8)	0.27	0.40,
No	53	50 (94.3)	3 (5.7)		0.09–1.82
EM + *3435CC*					
Yes	25	20 (80.0)	5 (20.0)	0.03	0.18,
No	67	64 (95.5)	3 (4.5)		0.04–0.85

We performed a multivariable regression analysis of factors affecting treatment outcomes, including age group (≥60 vs. <60), gender (female vs. male), the density of *H. pylori* (moderate and severe vs. mild), drinking alcohol (no vs. yes), smoking (no vs. yes), and CYP2C19 EM phenotype + *MDR1 3435CC* genotype (no vs. yes). The results suggested that sex and CYP2C19 EM phenotype + *MDR1 3435CC* genotype were related to the effects of *H. pylori* eradication treatment, respectively (p < 0.01, OR = 38.77, 95%CI: 3.98–377.09) and (p = 0.01, OR = 13.64, 95%CI: 1.73–107.19) (Table 6).

The treatment rate of *H. pylori* eradication in female patients with CYP2C19 EM and the *MDR1 3435CC* gen-

otype was 20.0%, significantly lower than that of female patients without both phenotypes and genotypes at 91.7% (p = 0.01, OR = 0.02, 95%CI: 0.00–0.45). However, there was no difference in the efficacy of *H. pylori* eradication treatment in male patients with the CYP2C19 EM phenotype + *MDR1 3435CC* genotype compared to the group without both phenotypes and genotypes, 90.4% vs. 94.7% (p = 1.00) (Table 7).

Table 6. Multivariate regression analysis of factors affecting the outcomes of *Helicobacter pylori* eradication treatment (n = 92).

Factor	OR	95% CI	P
Age: ≥60	4.41	0.20–94.74	0.34
Gender: female	38.77	3.98–377.09	<0.01
Density of *H. pylori*: moderate and severe	7.12	0.85–59.13	0.06
Drinking alcohol: yes	2.91	0.19–43.00	0.43
Smoking: yes	1.44	0.09–21.86	0.79
CYP2C19 EM phenotype + *MDR1 3435CC* genotype: yes	13.64	1.73–107.19	0.01

Table 7. Results of *Helicobacter pylori* eradication treatment in CYP2C19EM phenotype + *MDR1 3435CC* genotype by gender.

Factor	n	Eradication		p	OR, 95% CI
Male: EM and *3435CC*		**Success**	**Failure**		
Yes	20	19 (95.0)	1 (5.0)	1	0.71, 0.06–8.36
No	55	53 (96.4)	2 (3.6)		
Female: EM and *3435CC*					
Yes	5	1 (20.0)	4 (80.0)	0.01	0.02, 0.00–0.45
No	12	11 (91.7)	1 (8.3)		

The treatment rate of *H. pylori* eradication in female patients with CYP2C19 EM and the *MDR1 3435CC* genotype was 20.0%, significantly lower than that of female patients without both phenotypes and genotypes at 91.7% (p = 0.01, OR = 0.02, 95%CI: 0.00–0.45). However, there was no difference in the efficacy of *H. pylori* eradication treatment in male patients with the CYP2C19 EM phenotype + *MDR1 3435CC* genotype compared to the group without both phenotypes and genotypes, 90.4% vs. 94.7% (p = 1.00) (Table 7).

Discussion

The relationship between the CYP2C19 phenotype and the efficacy of *Helicobacter pylori* treatment

Research results showed that the rate of successful *H. pylori* eradication treatment in CYP2C19 EM phenotype is 87.5%, IM is 97.2%, and PM is 100%. There was no difference in the *H. pylori* eradication treatment rate between the CYP2C19 EM phenotypes compared with IM and IM + PM (p > 0.05). According to a study by Bui Huu Hoang on 186 patients - *H. pylori* eradication therapy was based on an antibiogram with the PPI drug esomeprazole; the results were consistent with several studies in Vietnam. The eradication rate of *H. pylori* success was not different between groups, and the phenotype of CYP2C19 EM was 84.7%, IM was 80.8%, and PM was 81.8%, with p > 0.05 (Hoang et al. 2017). According to research by Ho Tan Phat on 97 patients who had previously failed to get rid of *H. pylori*, the eradication rate increased while using the EBTM regimen (esomeprazole, bismuth, tetracycline, and metronidazole) for 14 days. Across groups of CYP2C19 phenotypes, effective *H. pylori* eradication did not vary (in patients with successful *H. pylori* eradication, the CYP2C19 EM phenotypic rate was 48.9%, IM phenotypic rate was 41.3%, and the PM phenotypic ratio was reported to be 48.9%, IM, and PM is 9.8%, with p > 0.05) (Phat et al. 2018).

Several studies worldwide had shown the influence of the CYP2C19 phenotype on *H. pylori* eradication treatment results. According to Okimoto T.'s research on *H. pylori* eradication treatment in 111 patients with gastric ulcer, duodenal ulcer, gastric ulcer/duodenal ulcer, atrophic gastritis, and gastric cancer with the RAC regimen (rabeprazole, amoxicillin, clarithromycin) for seven days, the success rate of *H. pylori* eradication treatment in the CYP2C19 EM phenotype was 69.7%, IM was 74.4%, and PM was 68.4%, CYP2C19 phenotype did not affect treatment outcome. In 108 patients treated for seven days with EAC regimens (esomeprazole, amoxicillin, and clarithromycin), the success rate in the CYP2C19 EM phenotype was 77.3%, the IM phenotype was 75.5%, and the PM phenotype was 71.4%; the CYP2C19 phenotype had no effect on treatment outcome (Okimoto et al. 2016). In research by Lin T.J. *H. pylori* eradication treatment in 88 patients with a 14-day serial regimen with the PPI drug rabeprazole, in the successful *H. pylori* eradication group, the phenotype rate of CYP2C19 EM was 41.77%, IM was 45.57%, and PM was 12.66%. In the failed *H. pylori* eradication therapy group, the phenotype rate of CYP2C19 EM was 66.67%, IM was 16.67%, and PM was 16.67%. The CYP2C19 phenotype did not affect the outcome of *H. pylori* treatment (Lin et al. 2018). The study of Auttajaroon J. treated over 100 patients with dyspeptic *H. pylori* infection for seven days (47 patients) and 14 days (53 patients) with an RBCL regimen (rabeprazole, bismuth, clarithromycin, and levofloxacin). The rate of successful *H. pylori* eradication in the group of patients treated for seven days in the CYP2C19 RM phenotype was 92.0%, IM was 81.0%, and PM was 100%. The rate of successful *H. pylori* eradication in the 14-day group of patients with the CYP2C19 RM phenotype was 96.3%, IM was 93.3%, and PM was 100%. The CYP2C19 phenotype did not affect the outcome of *H. pylori* treatment (Auttajaroon and Vilaichone 2019). Our results were consistent with the above studies. When using a bismuth 4-drug regimen with the proton pump inhibitor rabeprazole, the CYP2C19 phenotype did not affect the results of *H. pylori* treatment.

The relationship between the genotype of *MDR1 C3435T* and the effectiveness of treatment of *Helicobacter pylori*

The study results showed no difference in the successful *H. pylori* eradication treatment rate between genotypes *MDR1 3435CC* compared with *3435CT*, *3435TT*, and

3435CT + *3435TT*, respectively (p > 0.05). The research results were consistent with several studies worldwide on the influence of the *MDR1 C3435T* gene on the results of *H. pylori* eradication treatment. According to the Oh J.H. study on *H. pylori* eradication treatment on 210 patients with gastric ulcer, duodenal ulcer, gastritis infected with *H. pylori* with a three-drug regimen PAC (pantoprazole, amoxicillin, clarithromycin) for seven days; the successful eradication rate of *H. pylori* in patients with genotype *MDR1 3435CC*, *3435CT*, and *3435TT* was 82.7%, 84.4%, and 76.9%, respectively; there was no difference in the eradication treatment rate successful eradication of *H. pylori* among *MDR1* genotype groups *3435CC*, *3435CT*, and *3435TT*, with p > 0.05 (Oh et al. 2009). According to Gawronska-Szklarz B. study on *H. pylori* eradication treatment with a three-drug regimen of PAM (pantoprazole, amoxicillin, metronidazole) in 139 peptic ulcer patients infected with *H. pylori*, eradication treatment rate *H. pylori* success in patients with genotype *MDR1 3435CC* is 75.0%, *3435CT* is 73.77%, and *3435TT* is 73.53%; the rate of *H. pylori* eradication treatment failure in the group of patients with *genotype MDR1 3435CC* was 25.0%, *3435CT* was 26.23%, and *3435TT* was 26.47%. The results showed no difference in the *H. pylori* eradication treatment rate between the genotype groups *MDR1 C3435T*, with p > 0.05 (Gawronska-Szklarz et al. 2010). According to research by Karaca R.O. on 194 patients with duodenal ulcer and *H. pylori*-positive gastritis with a serial regimen (pantoprazole, bismuth, amoxicillin) for seven days and then (pantoprazole, metronidazole, bismuth, tetracycline) for seven days; in the group of successful *H. pylori* eradication treatment, the genotype rate of *MDR1 3435CC* was 16.1%, *3435CT* was 55.2%, and *3435TT* was 28.7%; in the group of failed *H. pylori* eradication, the genotype ratio of *MDR1 3435CC* was 33.3%, *3435CT* was 50.0%, and the *3435TT* genotype was 16.7%, there was no difference in the rate of successful *H. pylori* eradication treatment between genotype groups: *MDR1* genes *3435CC*, *3435CT*, and *3435TT*, with p > 0.05 (Karaca et al. 2017). Our study and the above studies showed that the *MDR1 C3435T* gene polymorphism did not affect the results of *H. pylori* eradication in patients with peptic ulcer disease using a PPI-containing regimen such as pantoprazole or rabeprazole.

The relationship between CYP2C19 phenotype + *MDR1 C3435T* genotype with the results of *Helicobacter pylori* eradication treatment

Patients without the CYP2C19 EM phenotype + *MDR1 3435CC* genotype had an *H. pylori* eradication outcome of 95.5% and 80% of the above phenotype + genotype (p = 0.03; OR = 0.18; 95%CI: 0.04–0.85). Multivariate logistic regression analysis, the results of *H. pylori* eradication treatment were different between the group with the CYP2C19 EM phenotype + *MDR1 3435CC* genotype and neither of the above phenotypes + genotypes (p = 0.01, OR) = 13.64, 95%CI: 1.73–107.19). In male patients, *H. pylori* eradication efficiency was higher than that of female patients (p < 0.01, OR = 38.77, 95%CI: 3.98–377.09). When analyzing the influence of the CYP2C19 EM phenotype + *MDR1 3435CC* genotype on the outcome of *H. pylori* eradication treatment by gender. In females with the CYP2C19 EM phenotype + *MDR1* genotype *3435CC*, the effectiveness of *H. pylori* eradication was reduced (p = 0.01, OR = 0.02, 95%CI: 0.00–0.45). *3435CC*, on the other hand, did not affect the outcome of *H. pylori* eradication treatment in men with CYP2C19 EM phenotype + *MDR1* genotype (p = 1.00). The findings were consistent with previous research on Oh J. H. *H. pylori* eradication treatment with the PAC regimen. In the successful *H. pylori* eradication group (57% male and 43% female), males had a higher successful *H. pylori* eradication rate than females (OR = 2.64, p = 0.01) (33). However, the author had not analyzed the influence of CYP2C19 EM phenotype + *MDR1 3435CC* genotype on the outcome of *H. pylori* eradication treatment by gender. We found no comparable studies in Vietnam or around the world to compare with our findings on the influence of CYP2C19 EM phenotype + *MDR1 3435CC* genotype on *H. pylori* results. According to Sugimoto M., the results of *H. pylori* eradication treatment were affected by many factors, such as antibiotic resistance to clarithromycin, metronidazole, levofloxacin, and amoxicillin of the *H. pylori* bacteria, the fast-metabolizing *CYP2C19* genotype, the *MDR1 3435CC* genotype of the patient, etc. (Sugimoto et al. 2014). In our study, the group of patients with the fast-metabolizing CYP2C19 phenotype (CYP2C19 EM) or the *MDR1 3435CC* genotype did not affect the outcome of *H. pylori* eradication when using the RBTT regimen. However, patients with both CYP2C19 EM phenotypes + *MDR1 3435CC* genotype had a lower rate of successful *H. pylori* eradication with RBTT regimens than patients without a concurrent phenotype + genotype. In these patients with the *MDR1 3435CC* genotype, the absorption of PPIs was reduced more than with genotypes *3435CT* and *3435TT*, possibly resulting in lower blood levels of the drug and leading to a poor inhibitory effected on the gastric acid secretion of PPIs. In patients with the CYP2C19 phenotype, EM metabolized PPIs more rapidly through the liver than the IM and PM phenotypes, resulting in lower blood concentrations of PPIs, resulting in less inhibition of gastric acid secretion compared with the IM and PM phenotypes. Therefore, when a patient has two CYP2C19 EM phenotypes + *MDR1 3435CC* genotype, it reduces the absorption of PPIs into the body and rapid metabolism of PPIs in the liver, leading to a decrease in blood concentration and decreased inhibition of gastric acid secretion, thereby reducing the effectiveness of *H. pylori* eradication therapy compared with people without both genotypes.

The strength of our study was to study both the *CYP2C19* gene and the *MDR1 C3435T* gene on the same duodenal ulcer patient. The news in our study was that the results showed that the female sex with both the CYP2C19 EM phenotype and the *MDR1 3435CC* genotype had lower effectiveness in *H. pylori* eradication than the group without both of the above phenotypes and genotypes. The weakness in our study was the low number of female patients.

Conclusion

The results of *H. pylori* eradication treatment in our study found that for female patients with the CYP2C19 EM phenotype + *MDR1 3435CC* genotype, the rate of *H. pylori* eradication treatment was lower than that of the group without both phenotype and genotype at the same time. In male patients, there was no difference in the efficacy of *H. pylori* eradication treatment in the CYP2C19 EM phenotype + *MDR1 3435CC* genotype compared with the control group. We recommend that in countries with a high ratio of CYP2C19 EM phenotype + *MDR1 3435CC* genotype, a low prognosis for *H. pylori* eradication should be observed. For female patients, more research is needed on the effect of CYP2C19 EM phenotype + *MDR1 3435CC* genotype on the results of *H. pylori* eradication treatment with a larger sample size.

Author contributions

Conceptualization, L.T.N., T.V.T. and V.B.N.; methodology, L.T.N., T.V.T. and V.B.N.; software, L.T.N., T.V.T. and V.B.N.; validation, L.T.N., T.V.T. and V.B.N.; formal analysis, L.T.N. and L.T.T.L.; investigation, L.T.N. and L.T.T.L.; resources, L.T.N. and L.T.T.L.; data curation, L.T.N. and L.T.T.L.; writing—original draft preparation, L.T.N.; writing—review and editing, L.T.N., M.H.T.P. and T.N.; visualization, L.T.N., M.H.T.P. and T.N.; supervision, L.T.N., L.T.T.L. and T.N.; project administration, L.T.N. and L.T.T.L.; funding acquisition, L.T.N. and L.T.T.L. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

The study was conducted following the Declaration of Helsinki, and approved by the Institutional Review Board of Vietnam Military Medical University (approval No. 1911/QĐ-HVQY dated 11 August 2015).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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