Effect of major CYP2C19 genetic polymorphisms on *Helicobacter pylori* eradication based on different treatment regimens

MALEK ZIHLIF[1], BANAN BASHAIREH[1], MOHAMMED RASHID[2], ZAID ALMADANI[1] and YAZUN JARRAR[3]

[1]Department of Pharmacology, [2]Department of Internal Medicine, Faculty of Medicine, The University of Jordan, Amman 11492; [3]Department of Pharmacy, Al-Zaytoonah University of Jordan, Amman 11731, Jordan

Abstract. *Helicobacter pylori* (*H. pylori*) infection is a global issue. Its eradication in affected individuals is important to prevent several further complications that may occur if left untreated. Proton pump inhibitors (PPIs) serve an important role in the eradication regimens of *H. pylori*. PPIs are metabolized primarily through the CYP2C19 enzyme in the liver. Inter-individual variation in the response to eradication treatment may partly be due to variations in the metabolism of PPIs. The aim of this study was to determine whether there was any association between CYP2C19 genetic polymorphisms and the response to eradication therapy amongst Jordanians infected with *H. pylori* receiving lansoprazole-based regimens. The present study was approved by the Institutional Review Board of The University of Jordan Hospital. A total of 141 patients infected with *H. pylori* were genotyped for the polymorphisms CYP2C19*2 and CYP2C19*17 using the PCR-restriction fragment length polymorphism assay method. Patients received lansoprazole-based triple or sequential therapy. The assessment of eradication was performed using either a *H. pylori* stool antigen test or from feedback from patients regarding their improvement. Eradication rates were 84.6% and 64.5% in the intermediate-metabolizer and extensive-metabolizer group, respectively. This difference was not statistically significant. Moreover, no significant association was found between the carriers of the CYP2C19*17 polymorphism and the response to eradication therapy. These findings suggest that there was no significant association between the CYP2C19 genotype and the response to eradication therapy amongst Jordanians infected with *H. pylori*.

Correspondence to: Professor Malek Zihlif, Department of Pharmacology, Faculty of Medicine, The University of Jordan, Queen Rania Street, Amman 11492, Jordan
E-mail: m.zihlif@ju.edu.jo

Introduction

Helicobacter pylori (*H. pylori*) infection is problem faced by individuals across the world. Half the world's population will be infected with this bacterium at least once throughout their life (1). *H. pylori* infection should be eradicated to prevent any further complications that may arise due to the effects of *H. pylori* on the gastric mucosa, such as chronic active gastritis, peptic ulceration, mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma (2). The majority of eradication regimens consist of proton pump inhibitors (PPIs) combined with two, antibiotics, including clarithromycin, metronidazole or amoxicillin (2). PPIs are acid-inhibitors used in the management of several gastrointestinal disorders. They act as irreversible inhibitors of the H^+/K^+ ATP enzyme system, thus affecting acid secretion in the gastric tract (3). The efficacy of numerous PPIs in the treatment of *H. pylori* infection varies amongst individuals, which may be partially related to variations in the PPI metabolic pathway (4). It has been shown that PPIs are primarily metabolized through CYP450 enzymes, particularly CYP2C19 (5). CYP2C19 is highly polymorphic, and >30 variant alleles have been identified (4).

In the Jordanian population, CYP2C19*2 is the principal defective allele (6), which is hypothesized to exhibit reduced enzymatic activity. A previously discovered defective allele for the CYP2C19 enzyme was CYP2C19*17, which is associated with increased enzymatic activity (7). A total of 4 phenotypes have been identified on the basis of PPI metabolism: Ultra-rapid metabolizers (homozygous and heterozygous for the mutant type, CYP2C19*17) (8), extensive metabolizers (homozygous for the wild type, CYP2C19*1), intermediate metabolizers [heterozygous; carrying one mutant allele (CYP2C19*2) and one wild type allele (CYP2C19*1)] and poor metabolizers (homozygous for the mutant type, CYP2C19*2) (4). There is no information available regarding the effect of the CYP2C19 genotype on the eradication of *H. pylori* amongst the Jordanian population to the best of our knowledge. Therefore, the aims of the present study were to determine the genotype and allele frequencies of CYP2C19*2 and CYP2C19*17 polymorphisms amongst Jordanian patients infected with *H. pylori*, and to determine whether there was a relation between these genetic polymorphisms and a patient's response to eradication therapy against *H. pylori*.

Materials and methods

Study design. This study was conducted in The Gastrointestinal Unit of The University of Jordan Hospital. Every patient provided signed informed consent to participate in this study. The study and the consent form were approved by the Institutional Review Board of The University of Jordan Hospital. Patients who had been diagnosed with *H. pylori* were interviewed after the completion of the endoscopy procedure, and the information related to each patient was recorded. Patients with *H. pylori* infection received either triple therapy or sequential therapy as shown in Table SI.

Study cohort. The study population were patients diagnosed with *H. pylori* infection using a Serim PyloriTek® Test kit (Serim Research Corporation) during the endoscopic procedure. The required sample size was calculated to be ~136 subjects, based on information from previous studies amongst Jordanians and using the Cochran's formula (9). In total of 230 *H. pylori* infected patients, without serious comorbidities, visited The University of Jordan Hospital in the previous year, according to the records of The Jordan University Hospital. It was calculated that a sample size of 139 patients would represent the *H. pylori* infected patients attending The University of Jordan Hospital using the power of test $1\text{-}\beta = 0.8$, 5% margin of error, and 95% confidence level.

The inclusion criteria of the patients were Jordanians aged between 17-75 years old who had a positive result on the Serim PyloriTek® Test. The exclusion criteria of the patients were: Patients with serious comorbidities, pregnant women, patients allergic to the amoxicillin, metronidazole or lansoprazole, and patients on other PPIs, such as omeprazole.

Accordingly, 149 patients were included in this study, 53.7% were females (n=80) and 46.3% were males (n=69). The age range of the patients was 17-73 years. Blood samples were collected from 141 patients and a stool test was obtained from 71 subjects. However, 17 patients were excluded from this study for the following reasons: 8 patients did not receive the chosen treatment regimens, and another 9 patients did not complete the treatment regimen.

Blood sample collection and extraction of genomic DNA. From each patient, 3-5 ml whole venous blood was collected in EDTA tubes and stored at 4°C. DNA was extracted from the whole blood using commercial kits for genomic DNA extraction (Wizard Genomic DNA Purification kit; Promega Corporation), according to manufacturer's protocol.

Genotyping of CYP2C19*2 (681G>A, rs42442850), CYP2C19*17 (-806C>T, rs12248560) alleles. Amplification of specific sites in the CYP2C19 gene containing the genetic variants of interest, CYP2C19*2 and CYP2C19*17, was performed as described by previously (10). The PCR condition were as follows: 200 ng extracted genomic DNA was amplified in a 20 μl reaction volume containing 0.5 mM $MgCl_2$, 1X Taq polymerase buffer (New England Biolabs, Inc.), 0.1 mM dNTPs, 15 pmoles each of the forward and reverse primers (Integrated DNA Technologies, Inc.), and 0.7 unit Taq DNA polymerase (New England Biolabs, Inc.). The thermocycling conditions were 94°C for 5 min; followed by 35 cycles of denaturation at 94°C for 45 sec, annealing at 55°C for 30 sec, and elongation at 72°C for 40 sec. The primer sequences were: CYP2C19*17 variant forward, 5'-AAATTTGTGTCTTCTGTTCTCAATG-3' and reverse, 5'-AGACCCTGGGAGAACAGGAC-3'; and CYP2C19*2 variant forward, 5'-CAGAGCTTGGCAATATTGTATC-3' and reverse, 5'-ATACGCAAGCAGTCACATAAC-3'.

The PCR products were digested by SmaI restriction enzyme (New England Biolabs, Inc.) at 25°C for 1 h for identification of the CYP2C19*2 allele. The PCR products were also incubated with the *Nsi*I restriction enzyme (New England Biolabs, Inc.) at 37°C overnight to detect the CYP2C19*17 allele (10).

The PCR products were separated on 1.5% agarose gel by applying an 125 A current for 20 min. The gel was stained by the Redsafe dye (Intron Biotechnology, Inc.).

Stool sample collection. Each patient was asked to bring a stool sample ≥1 month after completion of eradication therapy, this was used to determine whether the treatment for *H. pylori* infection had been successful. A positive result indicated a failure of the treatment and a negative result indicated success.

This test was performed using the Wondfo One Step *H. pylori* Feces Test (Wondfo, China; cat. no. WO6381115), according to the manufacturer's protocol. Briefly, the test kit contained a combination of *H. pylori* antibody coated particles and anti-mouse IgG antibody to qualitatively and selectively detect *H. pylori* antigens in stool samples. In the test line region of the kit, *H. pylori* antibody was immobilized. After the addition of the specimen into the test kit, the specimen was absorbed into the kit and mixed with the antibody-dye conjugate.

Statistical analysis. Normally distributed continuous variables, such as age, were analyzed using ANOVA followed by a Tukey's HSD post-hoc test. A Pearson's χ^2 and Fisher's exact test were used for independent variables to determine the association between CYP2C19*2 and CYP2C19*17 polymorphisms and response to eradication therapy, comparison between sequential and triple therapy, the association between response to eradication therapy and phenotypes.

$P<0.05$ was considered to indicate a statistically significant difference. Odds ratios for significant association were given with a 95% confidence interval. All statistical analyses were performed using SPSS Inc. version 23 (IBM Corp.).

Results

Genotype frequency of G681A and C-806T polymorphisms amongst Jordanians infected with H. pylori. For the CYP2C19 G681A genotype, the wild type genotype GG was seen (data not shown) in 118 patients (83.7%), the heterozygous genotype GA was seen in 23 patients (16.3%) and the homozygous variant genotype AA was not seen in any patient. Regarding the CYP2C19 C-806T genotype, the wild type genotype CC was seen (data not shown) in 79 patients (56%), the heterozygous genotype CT was seen in 53 patients (37.6%), and the homozygous variant genotype TT was seen in 9 patients (6.4%).

Accordingly, the majority of the patients (54.8%) in the present study carried the extensive-metabolizing phenotype

Table I. Distribution of the G681A genotype amongst responders and non-responders to eradication therapy based on the HpSA test and degree of symptoms.

Method of assessment	G681A genotype, n (%)		Total	P-value[a]
	GG	GA		
HpSA test				0.198
Responder	34 (51.5)	11 (16.7)	45	
Non-responder	19 (28.8)	2 (3.0)	21	
Total	53	13	66	
Reporting of symptoms				0.354
Complete improvement	37 (39.4)	3 (3.2)	40	
Partial improvement	21 (22.3)	5 (5.3)	26	
No improvement	24 (25.5)	4 (4.3)	28	
Total	82	12	94	

[a]Fischer's exact test. HpSA, *H. Pylori* stool antigen.

followed by the ultra-rapid-metabolizing phenotype (34%), whereas only a small percentage (8.5%) carried the extensive/intermediate-metabolizing phenotype. None of the patients carried the poor metabolizing phenotype.

Response to H. pylori eradication treatment. The response to eradication treatment of *H. pylori* was assessed using two methods; a *H. pylori* stool antigen (HpSA) test and improvement in symptoms after completion of treatment.

Out of 71 patients, 31% did not exhibit eradication of *H. pylori* and 69% responded to treatment. Follow up with patients was performed for 100 patients who already had symptoms. They were asked about the degree of symptom improvement after completion of treatment. Improvement was classified into three degrees: Complete improvement, partial improvement and no improvement. Out of the 100 patients, 30% exhibited no improvement of symptoms, whereas 70% showed some degree of improvement (27% had partial improvement and 43% had complete improvement). Correlation between the results of the HpSA test and symptoms improvement was performed for 60 patients. It was found that there was a significant association (Pearson's χ^2, P=0.013) between the HpSA test result and the degree of symptom improvement. Of the responders, based on the HpSA test, 73.8% showed improvement (partial or complete) of symptoms, and 61.1% of the non-responders showed no improvement of symptoms.

Patients who were infected with *H. pylori* were treated with either triple therapy or sequential therapy. The efficacy of the two regimens on the eradication of *H. pylori* based on the HpSA test results and the degree of improvement of symptoms were assessed. Accordingly, there was no significant difference in the efficacy of the two treatment regimens (Fisher's exact test, P>0.05). Amongst the non-responder group, 50% received triple therapy and 50% received sequential therapy, and amongst the responder group, 54% received triple therapy and 46% received sequential therapy. Additionally, there was no significant difference in the efficacy of the two treatment regimens depending on the patients' symptoms (Fisher's exact test, P>0.05). Amongst patients who did not improve, 60%

received triple therapy and 40% received sequential therapy. Amongst patients who improved completely, 55.8% received triple therapy and 44.2% received sequential therapy.

Association between the G681A polymorphism and response to eradication therapy. Next, whether there was a relation between the G681A polymorphism and the response to eradication therapy was assessed using the results of the HpSA test and the degree of improvement in symptoms. As shown in Table I, there was no significant difference the two CYP2C19 G681A genotypes GG and GA and the response to eradication therapy, using both the HpSA test and degree of the infections symptoms (Fisher's exact test, P>0.05) between.

Association between C-806T polymorphism with response to eradication therapy. No significant difference was found between the CYP2C19 C-806T genotypes CC, CT and TT and response to eradication therapy based on the HpSA and the degree of symptoms (Fisher's exact test, P>0.05; Table II).

Distribution of responders and non-responders to H. pylori eradication amongst the different CYP2C19 phenotypes based on the G681A and C-806T genotypes. The relationship between different CYP2C19 phenotypes and the response to eradication therapy was assessed. There was no significant difference between the different phenotypes of CYP2C19 metabolism and the response to *H. pylori* eradication based on the results of the HpSA test and the degree of *H. pylori* infection (Fisher's exact test, P>0.05; Table III).

Discussion

H. pylori infection is a common infection worldwide (1). Eradication of infection should be achieved to prevent further the complications when left untreated (11). All eradication regimens include the administration of PPIs, which play an important role in the treatment of *H. pylori* (12). However, eradication is not successful in several cases, due to various issues. One such issue is the variation in the metabolism of

Table II. Distribution of the C-806T genotype amongst responders and non-responders to eradication therapy based on HpSA test and the degree of symptoms.

Method of assessment	C-806Tgenotype, n (%)			Total	P-value[a]
	CC	CT	TT		
HpSA test					0.699
Responder	30 (45.5)	14 (21.2)	1 (15.0)	45	
Non-responder	15 (22.7)	5 (7.6)	1 (15.0)	21	
Total	45	19	2	66	
Reporting of symptoms					0.348
Complete improvement	20 (21.3)	19 (20.2)	1 (1.1)	40	
Partial improvement	16 (17.0)	9 (9.5)	1 (1.1)	26	
No improvement	20 (21.3)	8 (8.5)	0 (0.0)	28	
Total	56	36	2	94	

[a]Fischer's exact test. HpSA, *H. Pylori* stool antigen.

Table III. Distribution of the CYP2C19 phenotype amongst responders and non-responders based on the HpSA test and degree of symptoms.

Method of assessment	C-806Tgenotype, n (%)				Total	P-value[a]
	EM	Het.EM/IM	UM	Het.UM		
HpSA test						0.900
Responder	29 (44.0)	6 (9.1)	1 (1.5)	9 (13.6)	45	
Non-responder	13 (19.7)	2 (3.0)	1 (1.5)	5 (7.6)	21	
Total	12	8	2	14	66	
Reporting of symptoms						0.104
Complete improvement	19 (20.2)	2 (2.1)	1 (1.1)	18 (19.1)	40	
Partial improvement	11 (11.7)	5 (5.3)	1 (1.1)	9 (9.6)	26	
No improvement	20 (21.3)	2 (2.1)	0 (0.0)	6 (6.4)	28	
Total	50	9	2	33	94	

[a]Fischer's exact test. HpSA, *H. Pylori* stool antigen; EM, extensive metabolizers; IM, intermediate metabolizer; UM, Ultra-rapid metabolizer; Het, heterogenous.

the PPIs between patients (13). The present study revealed that ~30% of patients receiving the recommended therapy did not achieve eradication. This may be due to numerous factors other than CYP2C19 polymorphisms, such as age, nutritional status, sex, liver and kidney function, and concomitant medications and diseases (14). Several studies examined the effect of CYP2C19 polymorphisms (in particular G681A and C-806T) on the metabolism of lansoprazole; they reported that carriers of the G681A polymorphism exhibit a lower enzymatic capacity to metabolize lansoprazole, and thus, those subjects possess an increased ability to eradicate *H. pylori* (15,16). Conversely, other studies have reported that carriers of the C-806T polymorphism exhibit increased metabolizing activity of lansoprazole, thus, they are less likely to benefit from the standard dose of lansoprazole (17). However, there are no studies on the effect of these polymorphisms in the eradication of *H. pylori* infection amongst the Jordanian population.

Therefore, the aim of the present study was to investigate the effect of such polymorphisms on the response to eradication regimens. It was shown that there was a difference in the response to eradication therapy between extensive metabolizers (carrying the GG genotype) and intermediate metabolizers (carrying the GA genotype); the majority of patients that did not achieve eradication were extensive metabolizers, not intermediate metabolizers (90.5 vs. 9.5%, respectively). Additionally, amongst the extensive metabolizing individuals, it was shown that 35.8% were non-responders, whereas only 15.4% of the intermediate metabolizing patients were non-responders. However, these results were statistically insignificant. These results are similar to other previous studies where they found no significant effect on CYP2C19 genetic polymorphisms and the PPI response (18,19). These findings however also contradict several other studies that concluded that there was a significant relation between the G681A polymorphism and

response to eradication therapy based on lansoprazole (20,21). The difference in the results may be due to the small sample size included in the present study, and differences in ethnicities.

On the other hand, several studies have found similar results of what was observed in the present study (22,23). Although there are controversial results regarding the influence of the CYP2C19 genotype on the effects of PPIs, no association between CYP2C19 genotype and the eradication of *H. pylori* was observed in the present study. These results suggest that the CYP2C19 genotype is not a potential biomarker for determination of the proton pump response, at least amongst Jordanian patients.

There was no significant difference between the efficacy of the triple regimen and sequential regimen. Amongst non-responders, 50% received the triple regimen and the other 50% received the sequential regimen. Moreover, amongst responders, 54% received the triple regimen, whereas 46% received sequential therapy. Although these findings are in agreement with the findings of Gawrońska-Szklarz *et al* (23), they conflict with other studies and meta-analyses (24-26), which concluded that there was a significant difference between standard triple therapy and sequential therapy. Those studies showed that the sequential therapy achieved higher eradication rates compared to triple therapy. Regarding the assessment of response after eradication treatment, a significant association existed between the HpSA test results and the degree of symptom improvement; 73.8% of the responders showed improvement (partial or complete) of symptoms, and 61.1% of the non-responders showed no improvement of symptoms.

The frequency of the 681A mutant allele in Jordanian patients infected with *H. pylori* was found to be 8.2%. The mutant 681A allele frequency within different populations ranged from 7.8 to 45.5%. 681A allele frequency amongst several populations was similar to the Jordanian, including Russian (27), Italian (28), Norwegian (29), Egyptian (30) and Ethiopian (8) cohorts. Conversely, several other populations, including Faroese (31), Danish (31), African Americans (32). Chinese (33), Korean (34) and Japanese (10) showed significant differences in G681A allele frequencies compared with the Jordanian patients infected with *H. pylori*. Regarding the variant allele -806T, the frequency was found to be 25.2% in the present study population. This was similar to the allele frequency of Faroese (31), Danish (31), African American (32) and Norwegian (29). However, Chinese (8), Korean (34) and Japanese (10) showed a difference in the -806 allele frequency compared with the present study.

One of the limitations of the present study is the relatively small sample size of the *H. pylori* infected patients, which resulted in a lack of patients with a poor CYP2C19 metabolizer phenotype. This may result in a bias in the conclusions drawn regarding the influence of the CYP2C19 genotype on the response to lansoprazole. Further studies with larger cohorts of Jordanian patients are required to confirm the findings of the present study. In addition, this study did not investigate the association of CYP2C19 genotype with the patients morbidity and complications secondary to *H. pylori* infection. These clinical factors will be taken into consideration in the future studies regarding the influence of CYP2C19 genotype on lansoprazole response.

In conclusion, there was no significant association found between the CYP2C19 G681A and C-806T polymorphisms and the response to eradication therapy amongst Jordanian patients infected with *H. pylori*.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

BB conducted the experimental work. MR and ZA contributed to the clinical evaluation and analysis of the patients. BB, MZ and YJ analyzed the data. MZ and BB wrote this manuscript and YJ revised it. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Every patient provided signed informed consent to participate in this study. The study and the consent form were approved by the Institutional Review Board of The University of Jordan Hospital (Amman, Jordan).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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