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Research Paper

Eradication rate of *Helicobacter pylori* according to genotypes of *CYP2C19*, *IL-1B*, and *TNF-A*

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Background: Lansoprazole, amoxicillin, and clarithromycin are commonly used drugs for eradication of *Helicobacter pylori* (*H. pylori*). A few studies reported that the eradication rate was influenced by the functional polymorphism of *CYP2C19*, whose product metabolizes proton pomp inhibitors including lansoprazole.

Methods: This study examined the eradication rate among 67 participants in the polymorphism study who visited Daiko Medical Center, Nagoya University from July 2004 to October 2005. The participants aged 20 to 69 years were classified into three group according to *CYP2C19* genotype; rapid metabolizers (RM) with **1*1* genotype, intermediate metabolizers (IM) with **1*2* or **1*3* genotype, and poor metabolizers (PM) with **2*2, *2*3,* or **3*3* genotype. For the genotype classification, G681A (*681G* for **1* and *681A* for **2*) and G636A (*636G* for **1* and *636A* for **3*) were genotyped by PCR with confronting two-pair primers (PCR-CTPP). They were also genotyped for *IL-1B* T-31C and *TNF-A* T-1031C by a duplex PCR-CTPP.

Results: The eradication rate was 70.0% for RM, 93.9% for IM, and 85.7% for PM. The difference in the rate between RM and IM+PM was statistically significant (p=0.025). The eradication rate was highest for those with *IL-1B -31CC*; the p value was marginal among the whole subjects (χ^2=3.78, p=0.05) and not significant among the RM group (χ^2=1.60, p=0.21). The genotypes of *TNF-A* T-1031C had no associations with the eradication rate. But among the RM group, the odd ratio (OR) of the *TNF-A CT* for the eradication rate relative to *TT* was marginally reduced (OR=0.05, 95% confidence interval, 0.002-1.19).

Conclusions: The present study confirmed the low eradication rate for RM. The reproduced finding provides evidence that the *CYP2C19* genotype is useful to predict the success of the treatment. For the RM group, alternative regimens expected to be with a higher eradication rate will be recommended, especially to those with the *TNF-A -1031C* allele.

Key Words: Helicobacter pylori, Eradication, CYP2C19, IL-1B, TNF-A

1. Introduction

Helicobacter pylori (*H. pylori*) infection is an established cause of digestive diseases including ulcer, atrophic gastritis, stomach cancer, and mucosa-associated lymphoid tissue lymphoma [1-3]. Recent studies demonstrated that *H. pylori* eradication caused increase in platelets of patients with idiopathic thrombocytopenic purpura (ITP) [4,5]. Another study reported that the eradication may be useful to treatment of chronic urticaria, an autoimmune disease [6]. Arteriosclerosis is also presumed to be *H. pylori* –associated disease, though there is still controversy [7]. A study reported that infertility was associated with the seropositivity among men and women. In addition, they showed biological evidence that follicular fluid from infected women contained anti-*H. pylori* antibody, which reacted with spermatozoa [8].

In Japan, health insurance covers *H. pylori* tests and eradication treatment for digestive ulcers, but not for the other diseases. Since are convinced the effect of the eradication on ITP treatment and the possibility of stomach cancer prevention at least among those who are successfully treated for early stomach cancer [9], there are increasing demands for *H. pylori* eradication treatment in Japan. In an international workshop held in Sweden, "the majority of the scientific task force favored a search-and-treat strategy in first-degree relatives of gastric cancer patients and an overwhelming majority felt that a more general screen-and-treat strategy should be focused in the first instance on a population with a high incidence of *H. pylori*-associated diseases" [10], which may include Japan, a high stomach cancer incidence country. The eradication was reported to be effective to reduce the medical care costs in the United Kingdom [11], and in Japan [12]. These expert recommendations/opinions may partly justify the *H. pylori* eradication for the more generalized populations in Japan.

The treatments against *H. pylori* infection approved in Japanese health insurance are 7-day triple

therapies of lansoprazole (60mg) + amoxicillin (1,500mg) + clarithromycin (400mg) and omeprazole (40mg) + amoxicillin (1,500mg) + clarithromycin (800mg). The reported eradication rate for the former treatment was 87.5% in 96 patients with gastric ulcer and 91.1% in 90 patients with duodenal ulcer [13]. The rate for the latter treatment was reported to be 78.8% (n=113) by Kuwayama *et al* at the 7th annual scientific meeting of the Japanese Society of Helicobacter Research 2001. Since lansoprazole and omeprazole are metabolized by *CYP2C19* in the liver, the functional genotypes of *CYP2C19* could influence the eradication rate, as well as clarithromycin resistance of *H. pylori*. Concerning the lansoprazole-based triple therapy, there are two studies reporting the significant difference in the rate among those with different *CYP2C19* genotypes [14] or with the different genotype combinations of *CYP2C19* and *IL-1B* [15], while other studies showed no significant association [16,17]. It was reported that those with the *-511TT* genotype of *IL-1B* encoding interleukin 1β, a potent gastric acid inhibiting proinflammatory cytokine, had a higher eradication rate relative to those with the *-511CC* genotype [18].

This study aimed to examine the associations of the eradication rate with the functional polymorphisms of *CYP2C19* G681A (*2) and G636A (*3), *IL-1B* T-31C tightly linked with C-511T [19], and *TNF-A* T-1031C. Since TNF-α encoded by *TNF-A*, is also a proinflammatory cytokine inhibiting gastric acid secretion [20], we hypothesized that the functional polymorphism of *TNF-A* may influence the eradication rate. The *TNF-A* gene encoding TNF-α is known to have five polymorphism in the promoter region; G-238A, G-308A, C-857T, C-863A, and T-1031C. Among Japanese, the -238A and -308A alleles are rare and C-863A is tightly linked with T-1031C. With respect to *H. pylori* seropositivity, we have reported that the decreased OR of *TNF-A -1031CC* for *H. pylori* seropositivity relative to *TT* was significant, but the association with C-857T was not significant [21].

This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine (approval number 155) on June 16, 2004.

2. Subjects and methods

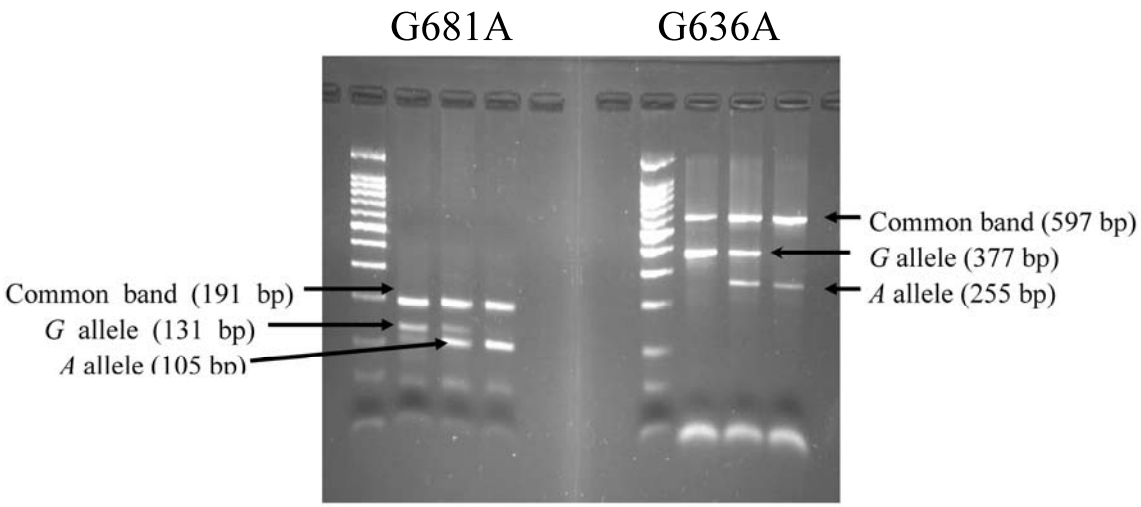
Study subjects

Subjects were sampled from those visited Daiko Medical Center, Nagoya University, Nagoya, Japan to seek *H. pylori* tests and eradication between July 2004 and October 2005. The visitors aged 20 to 69 years were asked to participate in the polymorphism study. Those who agreed with a written informed consent form to provide a 7ml of blood sample and to answer a questionnaire form on lifestyle including smoking habit, were enrolled in the present study. Any genotypes were not disclosed to the participants. The study protocol was approved by the ethics committee of the Nagoya University Graduate School of Medicine.

Treatment for H. pylori infection

Lansoprazole (30mg), amoxicillin (750mg), and clarithromycin (200mg) twice a day for 7 days (LAC regimen) were prescribed for those found to be infected with *H. pylori* by a ^{13}C-urea breath test or serum anti-*H. pylori* antibody. More than one month after the medication, a ^{13}C-urea breath test was conducted to examine the success/failure of the eradication treatment.

Figure 1. The agarose gel electrophoresis for polymorphism at G681A and G636A of *CYP2C19* by PCR with confronting.



Genotyping

DNA was extracted from the buffy coat by a BioRobot® EZ1 (QIAGEN Group, Tokyo) for genotyping *CYP2C19* G681A (*2) and G636A (*3), *IL-1B* T-31C, and *TNF-A* T-1031C. Genotypes were determined separately for the *CYP2C19* polymorphisms by polymerase chain reaction with confronting two-pair primers (PCR-CTPP) [22]. The primers for *CYP2C19* G681A and G636A were *2F1: 5′ AGA GCT TGG CAT ATT GTA TCT, *2R1: 5′ TAA GTA ATT TGT TAT GGG TTC C<u>C</u>, *2F2: 5′ CCA CTA TCA TTG ATT ATT TCC C<u>A</u>, *2R2: 5′ TCG ATT CTT GGT GTT CTT TTA C, and *3F1: 5′ AAC CAG CTA

GGC TGT AAT TGT, *3R1: 5′ CTT GGC CTT ACC TGG ATC, *3F2: 5′ ATT GTA AGC ACC CCC TGA, *3R2: 5′ CAC TGA TCA GGG AGC TAA TG, respectively. The underlined are the bases of the single nucleotide polymorphism. Genomic DNA (30ng to 100ng) was used per 25 μl of reaction with 0.18mM dNTPs, 12.5 pmol of each primer, 0.5 units of "AmpliTaq Gold", and 2.5 μl GeneAmp 10×PCR Buffer including 15mM $MgCl_2$ (Perkin-Elmer Corp., Foster City, CA). Amplification conditions were 10 minutes of initial denaturation at 95°C, followed by 30 cycles of 1 minute at 95°C, 1 minute at 59°C for G681A and 58°C for G636A, and 1 minute at 72°C, then a 5 minutes final extension at 72°C. The amplified DNA was visualized on a 2% agarose gel with ethidium bromide staining. A representative gel is shown in Fig. 1. The alleles were distinguished as follows: a 131-bp band for the *681G* allele and a 105-bp band for *681A* allele, with a 191-bp their common band, and a 377-bp band for *636G* allele and a 255-bp band for *636A* allele, with a 597-bp their common band. *IL-1B* T-31C and *TNF-A* T-1031C were genotyped with a duplex PCR-CTPP described previously [23].

Statistical analysis

Statistical analysis was performed using STATA Ver. 8 (College Station, TX) statistical software. The Hardy-Weinberg equilibrium, which indicates an absence of discrepancy between genotype and allele frequencies, was checked for the study subjects using a χ^2 test. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were adjusted for sex (dichotomous) and age (a continuous variable) using an unconditional logistic regression model.

3. Results

Table 1 describes the backgrounds of the whole visitors and participants.

From July 2004 to October 2005, 210 persons visited the center. Among them, 142 were found to be infected, 165 participated in the polymorphism study and LAC were prescribed for 93 participants with *H. pylori* infection (in fact, 97 were prescribed eradication drug but 4 subjected who failed the eradication by LAC at other clinics were excluded because we dosed them metronidazole instead of clarithromycin). The distribution of the *IL-1B* T-31C, *CYP2C19* G681A and G636A genes were in Hardy-Weinberg equilibrium (χ^2=0.83 and p=0.36, χ^2=0.72 and p=0.40, χ^2=0.54 and p=0.54, respectively), but the distribution of the *TNF-A* T-1031C gene was not (χ^2=4.05, p=0.04). The difference of the distributions between the expected and observed from the *TNF-A* T-1031C gene was not substantial; 128.3 for 131, 34.4 for 29, and 2.3 for 5. The participant subjects were classified into three groups according to *CYP2C19* genotype; rapid metabolizers (RM) with **1*1* genotype, intermediate metabolizers (IM) with **1*2* or **1*3* genotype, and poor metabolizers (PM) with **2*2, *2*3,* or **3*3* genotype; **1*1*, with the *681GG* and *636GG*; **1*2,* with the 681GA and *636GG; *1*3* with the *681GG* and *636GA; *2*2,* with the *681AA* and *636GG*; **2*3,* with the *681GA* and *636GA; *3*3,* with the *681GG* and *636AA*.

Table 1 Characteristics of the visitors and the participants in the polymorphism study

Characteristics		Visitors (n=210) n (%)	Participants (n=165) n (%)
Age	< 30 years	23 (11.0)	15 (9.1)
	31-49 years	52 (24.8)	42 (25.5)
	50-69 years	126 (60.0)	106 (64.2)
	70 < years	9 (4.3)	2 (1.2)
Sex	Males	91 (43.3)	74 (55.2)
	Females	119 (56.7)	91 (44.9)
Smoking[a]	Never	160 (76.6)	127 (77.0)
	Former	25 (12.0)	19 (11.5)
	Current	24 (11.5)	19 (11.5)
H. pylori[b]	Uninfected	65 (31.6)	55 (33.3)
	Infecteted	142 (68.6)	110 (66.8)
CYP2C19	RM	-	51 (30.9)
	IM	-	81 (49.1)
	PM	-	33 (20.0)
IL-1B C-31T[c]	*TT*	-	48 (29.3)
	CT	-	76 (46.3)
	CC	-	40 (24.4)
TNF-A C-1031T	*TT*	-	131 (79.4)
	CT	-	29 (17.6)
	CC	-	5 (3.0)

[a] The information on the status of smoking was not available for one subject. [b] Three subjects among visitors did not take the examination on *H. pylori* infection. [c] One subject was not genotyped

Table 2 The rate and odds ratios (ORs) of the eradication among the participants in the polymorphism study who were prescribed LAC and examined for the success/failure of the eradication.

Factors		Treated[a] n	Eradicated n (%)	OR[b] 95% CI
Total		67	57 (85.1)	
Age[c]	< 30 years	1	0 (0.0)	
	31-49 years	14	10 (71.4)	
	50-69 years	52	47 (90.4)	
	70 < years	0	-	
Sex	Females	33	29 (87.9)	1 (Reference)
	Males	34	28 (82.4)	0.69 (0.17-2.82)
CYP2C19	RM	20	14 (70.0)	1 (Reference)
	IM	33	31 (93.9)	6.69 (1.12-39.9)
	PM	14	12 (85.7)	4.35 (0.55-34.3)
	IM+PM	47	43 (91.5)	5.72 (1.24-26.3)
IL-1B	*-31TT*	17	13 (76.5)	1 (Reference)
	-31CT	36	30 (83.3)	1.36 (0.31-5.96)
	-31CC	14	14 (100)	∞[e]
IL-1B[d]	*-31TT*	5	3 (60.0)	1 (Reference)
	-31CT	12	8 (66.7)	0.45 (0.03-7.99)
	-31CC	3	3 (100)	∞[f]
TNF-A	*-1031TT*	51	45 (85.1)	1 (Reference)
	-1031CT	14	10 (71.4)	0.33 (0.07-1.51)
	-1031CC	2	2 (100)	∞[g]
TNF-A[d]	*-1031TT*	16	13 (81.3)	1 (Reference)
	-1031CT	4	1 (25.0)	0.05 (0.002-1.19)
	-1031CC	0	-	-
Smoking	Never	49	43 (87.8)	1 (Reference)
	Former	12	9 (75.0)	0.49 (0.08-3.00)
	Current	6	5 (83.3)	0.82 (0.07-10.0)
Smoking[d]	Never	16	12 (75.0)	1 (Reference)
	Former	4	2 (50.0)	2.16 (0.12-40.5)
	Current	0	-	-

[a] participants in the polymorphism study who were prescribed LAC and examined for the success/failure of the eradication. [b] adjusted for sex and

age. [c] p=0.012 for 2 by 3 table using a χ^2 test. [d] Among the participants with the rapid metabolism. [e,f,g] Compared with reference by a χ^2 test, the p values were 0.05, 0.21 and 0.61, respectively

Table 2 shows the eradication rate for 67 participants in the polymorphism study who were prescribed LAC and examined for the success/failure of the eradication. The combination of *CYP2C19* IM and PM had a significantly high rate relative to RM. The eradication rate was highest for those with *IL-1B -31CC* but the p value was marginal (χ^2=3.78, p=0.05). There were no differences in the eradication rate among those with different genotypes of *TNF-A* T-1031C. Among the rapid metabolizers, however, the decreased OR of *TNF-A CT* relative to *TT* was marginal (OR=0.05, 95% CI, 0.002-1.19). The OR for current and former smokers at the first visit was 0.82 (95% CI, 0.07-10.0) and 0.49 (95% CI, 0.08-3.00), respectively. During the medication, two out of six current smokers quit smoking, three continued smoking, and one did not answer about smoking habit.

4. Discussion

In the present study, *CYP2C19* IM+PM showed a significantly high eradication rate relative to RM. Among the 10 failed, 6 were RM. The *IL-1B* T-31C polymorphism was associated with the eradication rate. Smoking during non-medication period did not affect the eradication rate. This was the first report on the possible association between the *TNF-A* polymorphism and the eradication rate among those with RM.

The percentage of RM among those infected with *H. pylori* (31.2%) was similar to that of Japanese populations; by Furuta *et al* (32.6% of 141 subjects) [14], by Take *et al* (32.5% of 249 subjects) [15], by Kawabata *et al* (41.3% of 80 subjects) [16], and by Sugimoto *et al* (38.1% of 315 controls infected with *H. pylori*) [24]. Those percentages are much lower than those in Europe (81.1% of 143 subjects in Italy [25] and 73.3% of 60 subjects in Germany [26]). The allele frequencies for *IL-1B -31T* (0.536) and *TNF-A -1031T* (0.871) in this study were also similar to those among Japanese (0.558 of 1,062 chromosomes [27], and 0.835 of 2,742 chromosomes [21], respectively), and lower and higher than that in Italy (0.669 and 0.768 of 1,288 chromosomes, respectively) [28].

To date, four studies examined the association of the eradication rate with the *CYP2C19* genotypes. Two studies demonstrated non-significant results contrary to ours; in a randomized controlled study of lansoprazole versus rabeprazole for 187 patients with digestive ulcer by Kawabata *et al* [16], the eradication rate was 73% for 33 RM, 74% for 35 IM, and 83% for 12 PM in the LAC group, and in the study by Miki *et al* [17], 83% for 12 RM, 85% for 26 IM, and 78% for 9 PM. Although the corresponding association is controversial, our present study confirmed that the RM group relatively resistant to LAC should be treated with a more effective alternative regimen. Accordingly, the genotyping of *CYP2C19* before eradication treatment could be useful to avoid the failure of treatment.

The present study indicated that the polymorphism of *IL-1B* T-31C tightly linked with C-511T is one of the determinants on the result of *H. pylori* eradication. Among the RM group, *IL-1B -31CC* tended to show the highest eradication rate but the p value was not significant (χ^2=1.60, p=0.21). Although the association with combinations of *CYP2C19* and *IL-1B* C-511T was reported [15], our data did not reach significance, probably due to the small number of subjects analyzed.

TNF-A T-1031C did not provide useful information to predict the result of the eradication treatment. But among the RM group, *TNF-A* T-1031C was useful as the indication of the success/failure of the eradication. *TNF-A* C-863A polymorphism linked tightly to T-1031C affects TNF-α expression; *-863 A* was associated with a lower serum TNF-α level.[29] Previously we have reported that *TNF-A -1031TT* was associated with persistent *H. pylori* infection and hypothesized that *TNF-A -1031TT* produces the high level of TNF-α, resulting in low gastric acid [21]. This study also indicated that those with the RM and *TNF-A -1031CT* genotype could not suppress gastric acid enough to eradicate *H. pylori*. Because this result was based on the small numbers, studies of a larger size are needed to confirm our finding.

The problem of clarithromycin-resistant *H. pylori* is substantial in the eradication, but we could not determine the drug resistance because endoscopy was not conducted in our clinic. This is one of the limitations of this study. It was reported that the eradication rate was quite low among the RM group infected with clarithromycin-resistant *H. pylori* [14]. Take *et al* reported that in a mulitivariate analysis, susceptibility to clarithromycin and *CYP2C19* were significant factors, with *IL-1B* C-511T and smoking not significant, but the association of *CYP2C19* genotype was marked only among those with *IL-1B -511CC* [15]. The relation between the *TNF-A* genotype and the eradication rate according to the status of *H. pylori* drug resistance remains to be elucidated.

It has been well documented that smokers had a lower success probability of the eradication [30-32]. On the other hand, smokers who quit smoking during the medication reportedly had a higher eradication rate [32]. We strongly recommended to quit smoking during the medication, so two quit smoking at least during the medication and succeeded in *H. pylori* eradication. Since the smokers during the medication were four at most, eradication rate for smokers could not be estimated with an enough statistical power.

In conclusion, the present study confirmed the low eradication rate among the RM who were treated with LAC. The reproduced finding provides evidence that the *CYP2C19* and *IL-1B* genotype are useful to predict the success of the treatment. For the RM group, alternative regimens expected to be with a higher eradication rate will be recommended especially to those with the *TNF-A -1031C* allele. Further biological

investigation will be required to elucidate the association of these polymorphisms and the eradication rate. Based on the finding, we began in November 2005 to inform the participants of the *CYP2C19* genotype to recommend another triple therapy (rabeprazole, metronidazole, and amoxicillin) for those with RM [16,33].

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Conflicts of interest

The authors have declared that no conflict of interest exists.

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