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Influence of inflammatory cytokine polymorphisms on eradication rates of *Helicobacter pylori*

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Abstract

Pro-inflammatory cytokines and anti-inflammatory cytokines are produced in gastric mucosa from inflammatory cells activated by *Helicobacter pylori* (*H. pylori*) infection. Of the inflammatory cytokines, interleukin (IL)-1 β and tumor necrosis factor (TNF)- α have a potent inhibitive effect on gastric acid production. Polymorphisms in these genes are associated with individual differences in cytokine messenger RNA levels, which result in different gastric mucosal inflammation, different acid inhibition and different gastroduodenal disease risks in response to *H. pylori* infection. The sustained higher intragastric pH during an eradication therapy is known to be one of the therapeutic determinants of the *H. pylori* eradication as well as antibiotics resistance and poor compliance. The *IL-1B*-511 polymorphism is related to eradication rate, and, in combined analysis of previous reports, the eradication rate in patients with the *IL-1B*-511 C/C genotype (77.4%, 209/270), low IL-1 β producer genotype, is lower than that of the *IL-1B*-511 C/T and T/T genotypes (87.2%, 631/724) (Odds ratio for eradication failure: 1.98, 95% confidence interval: 1.38–2.84, $P = 0.0002$). Moreover, the odds ratio of combined CYP2C19 rapid metabolizer-*IL-1B*-511 C/C type for eradication failure is 11.15 (5.23–23.78) times that of the CYP2C19 poor metabolizer-*IL-1B*-511 non-C/C type. However, there is no positive data indicating the role of other inflammatory cytokine polymorphisms (e.g. *IL-1RN*, *TNF-A* or *IL-10*) in eradication therapy. Nevertheless, the studies show that inflammatory cytokine polymorphisms, especially the *IL-1B*-511 T/T genotype, are the determinants of eradication by affecting gastric acid secretion and mucosal inflammation. Therefore, the tailored eradication therapy, considering inflammatory cytokine polymorphisms, may be effective for the higher eradication rates.

Keywords

eradication therapy; *Helicobacter pylori*; IL-1 β ; inflammatory cytokine; polymorphism; TNF- α

1. Introduction

Helicobacter pylori (*H. pylori*) is such an ancient bacteria that its genetic variations can be used to trace migrations during the past 100 000 years. In fact, it is now believed that

humans probably acquired *H. pylori* quite early in their history, long before the migration of modern humans out of Africa.^{1,2} *H. pylori* colonize the gastric mucosa in human populations with a prevalence that ranges from approximately 25% in developed countries to as high as 80–95% in developing countries.^{3–5} Therefore, for the prevention of the development of *H. pylori*-related diseases, an eradication therapy of *H. pylori* has been carried out not only for the patients with *H. pylori*-related upper gastrointestinal diseases (e.g. peptic ulcer diseases, gastric adenoma, and gastric-mucosa-associated lymphoid tissue lymphoma), but also for the patients with some extra-gastrointestinal disorders (e.g. such as idiopathic thrombocytopenic purpura, chronic idiopathic urticaria and iron-deficiency anemia).^{6–12} Currently, the eradication of *H. pylori* is known to be an important strategy for the prevention of gastric cancer development.^{6,8,13} As with other bacterial infections, however, successful treatment of *H. pylori* infection depends on the use of antibiotics to which the organism is susceptible. Additionally, the cure rate is also affected by several major factors, such as genotypes of host genetic factors (e.g. CYP2C19 and multidrug-resistant transporter-1 [MDR1]), lifestyle (smoking habits), treatment compliance, duration of eradication therapy, *H. pylori* virulent factors and gastric emptying.^{14–17} Moreover, the importance of potent acid inhibition during eradication therapy has recently been demonstrated.^{18–20}

H. pylori virulence factors (e.g. *cagA* and *vacA*) play important roles in gastric mucosal inflammation and injury in relation to activated inflammatory cell infiltration.^{21,22} Activated neutrophils and mononuclear cells infiltrating into gastric mucosa with *H. pylori* infection produce several pro-inflammatory cytokines (e.g. interleukin [IL]-1 β , IL-6, IL-8 and tumor necrosis factor [TNF]- α) and anti-inflammatory cytokines (e.g. IL-4 and IL-10). The *cagA*-positive, *vacA* s1 and m1 strains produce significantly higher IL-1 β in gastric mucosa compared with that of *cagA*-negative, *vacA* s2 and m2 strains.^{23,24} Interestingly, IL-1 β and TNF- α are potent inhibitors of gastric acid secretion.²⁵ Therefore, the increased gastric mucosal production of IL-1 β and/or TNF- α in response to *H. pylori* infection results in a potent suppression of gastric acid secretion, as well as an enhanced gastric mucosal inflammation.^{26–29}

With the abovementioned evidences, it raises the question of whether the cure rates of *H. pylori* eradication are associated with the pro-inflammatory cytokine polymorphisms.^{30–33} Therefore, we decided to review the association of *H. pylori* infection and inflammatory cytokines, the roles of cytokine gene polymorphisms for gastric mucosal changes, and then summarize the efficacy of sufficient acid inhibition during the eradication in relation to inflammatory cytokine gene polymorphisms.

II. Inflammatory cytokine and *H. pylori* infection

The key physiological event in *H. pylori* infection is the initiation of a gastric mucosal inflammatory response. *H. pylori*, its products and many non-microbial agents stimulate transcription and synthesis of inflammatory cytokines, especially in IL-1 β and TNF- α . Inflammatory cytokines are soluble peptide molecules that mediate the interaction between immunocompetent and hematopoietic cells, and between the immune and neuroendocrine systems.³⁴ After *H. pylori* infects the gastric mucosa, neutrophils and mononuclear cells activated by *H. pylori* infection infiltrate the gastric mucosa, and produce several inflammatory cytokines.³⁵ These cytokines exert their biological effects through binding to specific receptors on target cells.

Of the inflammatory cytokines, IL-1 β and TNF- α , which are produced locally in the gastric mucosa, are potent inhibitors of gastric acid secretion.^{25,36,37} IL-1 β is 100 times more potent an inhibitor than a proton pump inhibitor (PPI), and 6000 times more potent than

histamine-2 receptor antagonists on a molar basis.^{25,36} The intracisternal injection of IL-1 β induces longstanding inhibition of gastric acid secretion, an effect that is dependent on the integrity of the prostaglandin (PG) pathways, in particular PGE2.³⁸ As a biological mechanism, IL-1 β stimulates gastrin release from gastric G cells and histamine release in resting fundic enterochromaffin-like (ECL) cells, whereas pre-incubation of these cells with the cytokine markedly inhibits gastrin-stimulated histamine secretion.^{39,40} This modulation of the physiological function of G cells and ECL cells by IL-1 β can explain the hypergastrinemia and the decreased gastric mucosal histamine levels as observed in *H. pylori*-induced gastritis. IL-1 β also has profound effects on parietal cells. For example, IL-1 β modulates parietal cells transcription of the H,K-ATPase α -subunit gene via an ERK1/2 kinase signal pathway by *H. pylori* infection. Moreover, in animal studies, decreased acid secretion is reported to be accompanied by an elevation of IL-1 β mRNA levels in the *H. pylori*-infected gastric mucosa, and the effect is reversed after injection of an IL-1 endogenous receptor antagonist.²⁶ TNF- α is reported to have many pathways of gastric acid inhibition.⁴¹ This inhibition occurs at the post-receptor level and involves pertussis toxin and tyrosine kinase dependent and independent pathways. Therefore, the increased production of IL-1 β and/or TNF- α in gastric mucosa by *H. pylori* infection results in enhanced gastric acid suppression.^{26–29}

III. Inflammatory cytokine polymorphism of IL-1 β and TNF- α

Most inflammatory cytokine genes have genetic variations, which influence cytokine production into gastric mucosa.

The *IL-1B* gene has three diallelic polymorphisms at positions -511, -31, and +3954 base pairs (bp) from the transcriptional start site.⁴² The gene for *IL-1 receptor antagonist (IL-RN)* has a variable number of identical tandem repeats of 86 bp in length in intron 2.⁴³ The mucosal IL-1 β levels significantly differ among different genotypes of *IL-1B*-511, -31 and *IL-RN*. Moreover, the carriers of the *IL-1B*-511 T, -31 C and *IL-RN* *2 allele have significantly higher IL-1 β levels than carriers of the other genotype.³⁵ According to this difference, *H. pylori*-infected carriers with the *IL-1B*-511 T allele have lower levels of gastric acid secretion compared with those with the *IL-1B*-511 C allele.²⁸ Furuta *et al.*²⁹ reported that the fasting intragastric pH is 6.5 in *H. pylori*-positive patients with the *IL-1B*-511 T/T genotype and 3.8 in those with the C/T genotype, which is significantly higher than those with the C/C genotype (i.e. pH 2.4). Moreover, in histology, the scores for inflammatory cell infiltration are significantly higher in the carriers of the *IL-1B*-511 T/T genotype than those of the T/C or C/C genotype.²⁹ A difference also occurred in the score of neutrophil infiltration between *IL-1RN**1/*1 and *IL-1RN**1/*2 genotypes. Although there is some controversy,⁴⁴ recent epidemiological studies have revealed that the carriers of the *IL-1B*-511 T, *IL-1B*-31 C allele or *IL-1RN* *2/*2 (2 repeats of 86 bp) genotypes, high producer alleles/genotypes, have an increased risk of gastric atrophy, peptic ulcer and gastric cancer compared with those with the *IL-1B*-511C, *IL-1B*-31 T or non-*IL-1RN**2 alleles.^{28,29,35,37,45} The combination of *IL-1B* and *IL-1RN* genotypes additively increases gastroduodenal disease risks as well as histological gastric mucosal inflammation risks.²⁹ Increased IL-1 levels will theoretically result in enhanced suppression of gastric acid secretion allowing more rapid development of gastric atrophy and an increased risk of developing gastric cancer.

TNF-A encodes TNF- α , and is polymorphic.^{46,47} The *TNF-A*-238 G/A and -308 G/A polymorphisms are relevant to different transcriptional intra-individual activities, and these polymorphisms are associated with the development of duodenal ulcers, gastric ulcers and gastric cancers, as observed in various inflammatory and autoimmune diseases in Western populations.^{46,47} However, these polymorphisms are not found in Asian populations because

most of their patients have lower producer alleles, *TNF-A*-238 G/G and -308 G/G genotypes.^{48–50} Recently, three polymorphisms of the *TNF-A*-1031 T/C, -863 C/A, and -857 C/T, which are related to high transcriptional promoter activity, have been identified in Japanese patients.^{51,52} Concanavalin A-stimulated TNF- α production from peripheral mononuclear cells in subjects with the *TNF-A*-857/-863/-1031 TAC haplotype is 1.8-fold higher than in subjects with dominant genotypes.⁵¹ In fact, *TNF-A*-857/-863/-1031 TAC genotypes are correlated with rugal hyperplastic gastritis, peptic ulcer and gastric cancer developments.^{48–50}

Thus, on a theoretical basis, the polymorphisms of these inflammatory cytokines, not only *IL-1B*, *IL-1RN* and *TNF-A*, but also *IL-8*⁵³ and *IL-10*⁵⁴ might be related to the intraindividual differences in gastric mucosal inflammation and gastric acid inhibition in response to *H. pylori* infection.

IV. Gastric acid and eradication therapy

Recently, *H. pylori* eradication rates of the traditional clarithromycin (CAM)-containing triple therapy have steadily been eroded over time largely due to the increasing prevalence of the CAM-resistant strain (resistance rate: more than 20–25%), because of the increasing usage chance of CAM (e.g. chronic obstructive pulmonary diseases and chronic otitis media).⁵⁵ Therefore, the current recommended therapies that increase the success rates of initial treatments are sequential therapies (sequential administration of a dual therapy PPI plus amoxicillin [AMPC] for 5 days followed by the PPI plus CAM and tinidazole or metronidazole for 5 days), bismuth-containing quadruple therapy and therapy with a PPI plus AMPC, CAM and tinidazole or metronidazole (MNZ) for 7–14 days.⁵⁶

An insufficient gastric acid inhibition during the eradication treatment also causes eradication failure. CAM and AMPC, which are key antibiotics of the *H. pylori* eradication regimen, are acid-sensitive, and therefore, the gastric acid secretion must be potently inhibited during the treatment for preventing their degradation under a low pH condition.²⁰ The potent acid inhibition by acid inhibitory drugs makes antibiotics more stable and bioavailable in the stomach and increases the concentration of antibiotics in gastric mucosa.^{57–59} Raising pH from 3.5 to 5.5 increases the *in vitro* effectiveness of AMPC more than 10-fold.⁵⁷ Moreover, acid inhibition allows *H. pylori* to reach the growth phase and become more sensitive to antibiotics, such as AMPC.⁵⁹

In dual therapy with omeprazole (OPZ) 20 mg bid and AMPC 1 g bid for 7 days, sustained intragastric pH (> 5.5) levels during eradication therapy are reported to be required for therapeutic success.⁶⁰ The success rates of triple eradication therapy are also closely related to the degree of acid suppression during treatment irrespective of adding a second antibiotic (Fig. 1a,b).²⁰ In cases with a percentage time of intragastric pH < 4.0 and an average 24-hour intragastric pH less than 10% and more than 6.0, respectively, the majority of patients can overcome *H. pylori* infection irrespective of their bacterial susceptibility to CAM in triple therapy with lansoprazole (LPZ), CAM and AMPC (Fig. 2).²⁰

This raises the question of which regimen of eradication reveals a sufficient acid inhibition throughout a 24-hour period. Recently, Villoria *et al.*⁶¹ reported a meta-analysis asking whether high-dose PPI (2-times-doses twice daily dosing) increase cure rates of triple eradication therapy consisting of a PPI and CAM plus AMPC or tinidazole/MNZ for 7 days. The intention-to-treat cure rate is 82% with the high-dose PPI regimen compared to 74% with standard (relative risk: 1.09; 95% confidence interval (CI): 1.01–1.17). Therefore, the high-dose PPI regime seems more effective than the standard-dose regime, suggesting that increased PPI doses have additive effects.⁶¹ However, the cure rate with the high-dose PPI therapy is poor, less than 85%. The half-life of most PPI, OPZ, LPZ and rabeprazole (RPZ),

is 2–3 hours, and therefore, PPI are rapidly eliminated from the systemic circulation after 2–3 hours. Then, the $H^+,K^+ATPase$ newly generated or activated in gastric parietal cells after rapid elimination of PPI can secrete gastric acid. To overcome this situation, the usefulness of high frequent PPI dosing regimen is being considered, and, in fact, the four-time-daily dosing therapy of PPI plus AMPC is reported to attain high re-eradication rates (96.8–100%).⁶² High frequent PPI dosing sustains a higher PPI level throughout a 24-hour period and can continue to inactivate $H^+,K^+ATPase$ for 24 hours with high frequent PPI, resulting in sufficient acid inhibition.⁶³

Moreover, the effects of PPI depend on metabolic enzyme, cytochrome P450 (CYP) enzymes, and CYP2C19 with genetic differences in the activity of this enzyme.⁶⁴ In rapid metabolizers (RM) of CYP2C19, PPI are rapidly eliminated from the systemic circulation, and therefore, acid inhibition attained by a PPI in the RM genotype is often insufficient in comparison with poor metabolizers (PM).^{18,63,65,66} The CYP2C19-related differences in acid inhibition attained influence eradication rates by a PPI-based regimen. The eradication rate by a triple therapy for 1 week in RM is significantly lower in comparison with those attained in PM (72.7% in RM and 97.8% in PM).⁶⁷ This analysis also supports the theory that potent acid inhibition is required for treatment to be successful.

Therefore, physicians are recommended not to increase the dosing of PPI at one time, but to build an optimal regimen by considering CYP2C19 polymorphisms, a PPI dosing schedule, and other factors influencing gastric acid secretion (e.g. cytokine polymorphism) in each patient as well as antibiotics-resistance. In RM, the intragastric pH value with RPZ 10 mg qid, not 20 mg bid or 40 mg oia, could keep intragastric pH > 4.0 throughout a 24-hour period.⁶³

V. Inflammatory cytokine polymorphism and eradication therapy

In 2003, although Take *et al.*³⁰ reported the association with the *IL-1B*-511 polymorphism and eradication therapy for *H. pylori* infection, there was no significant difference in the cure rates between different *IL-1B*-511 genotype groups (Table 1). However, the cure rate of 1-week triple OPZ-AMPZ-CAM therapy by different *IL-1B*-511 genotypes is influenced in CYP2C19 genotype status, especially in the *IL-1B*-511 C/C genotype. These findings suggest that the *IL-1B*-511 polymorphism affects eradication therapy through gastric acid inhibition.³⁰

Furuta *et al.*³¹ and Sugimoto *et al.*³² reported that the *IL-1B*-511 polymorphism is associated with different acid inhibition levels in response to *H. pylori* infection as well as *H. pylori* eradication rates. The eradication rates in patients with *IL-1B*-511 C/C, C/T and T/T genotypes are 72%, 87% and 88%, respectively ($P = 0.0017$).³² In patients infected with CAM-resistant strains, the *IL-1B*-511 T/T genotype significantly increases the eradication rate to 78%, which appears greater than for those with the *IL-1B*-511 C/C and C/T genotypes (35% and 50%, respectively).³¹ On the other hand, Ishida *et al.*⁶⁸ and Zambon *et al.*³³ reported no significant association with the *IL-1B*-31 genotypes or with the cure rate for eradication therapy. In a former report by Ishida *et al.*,⁶⁸ although the eradication rate is highest for that with the *IL-1B*-31C/C genotype tightly linked with the *IL-1B*-511 T/T genotype, the P -value is marginal among the whole subjects. The sample sizes of these two studies are small, and therefore it will likely be difficult to show statistically significant differences among different genotypes.

When the *IL-1B*-31 T/C polymorphism is displaced in *IL-1B*-511 C/T, because the polymorphism of *IL-1B* T-31C is tightly linked with 511 C/T, the *IL-1B*-511 polymorphisms significantly influence the eradication rates using data of previous reports (Fig. 3).^{30–33,68} The *H. pylori* eradication rate in the *IL-1B*-511 C/C genotype is 77.4% (209/270, 95%CI:

71.9–92.3%), which is significantly lower than *IL-1B*-511 C/T and T/T genotypes (87.2%, 631/724, 95%CI: 84.5–89.5%, $P = 0.0002$) (Fig. 3). The risk of failure for eradication therapy in the *IL-1B*-511 C/C genotype is 1.98 (95%CI: 1.38–2.84, $P = 0.0002$) times that of the *IL-1B*-511 C/T and T/T genotypes, and therefore the *IL-1B*-511 C/C genotype is considered to be a risk factor for eradication failure.

There are no significant relationships between the eradication rates and polymorphisms of *TNF-A*-857/-863/-1031 and *IL-10*-1082/-819/-592 (Table 1).^{32,68} Zambon *et al.*³³ reported that a significant association was found between the *IL-10*-819 or *IL-10*-592 polymorphism and eradication success: the *IL-10*-819 T/T or *IL-10*-592 A/A genotypes are more frequently found among patients with eradication (13.3%) than among subjects without eradication (1.8%). Moreover, a significant association is found among the cure rate for CAM-sensitive strains and the *IL-12B*+15485 polymorphism (e.g. C/C genotype: absent for eradicated patients and 13.3% for not eradicated subjects) and *TNF-A*-238 genotypes.³³ However, the sample size of this report is too small and statistical analysis seems to have many mistakes. Anyway, *TNF-α* also inhibits basal gastric acid and histamine secretions, and gastrin- and carbachol-stimulated acid secretions of gastric parietal cells in a dose-dependent manner.⁴¹ *IL-10* is a multifunctional anti-inflammatory cytokine that inhibits the production of pro-inflammatory cytokine by inhibition of Th1 lymphocytes and stimulation of B lymphocytes and Th2 lymphocytes.^{69,70} Although *TNF-α* potentially upregulates the active inflammation of gastric mucosa and *IL-10* decreases *TNF-α* and *IL-1* productions in gastric mucosa, the acid inhibition-related effects of *TNF-α* and *IL-10* may not be as potent as that of *IL-1β*.

H. pylori virulence factors (e.g. *cagA* and *vacA*) play important roles in gastric mucosal injury in relation to inflammatory cytokine production.^{21,22} The cure rates in patients infected with *cagA*-positive and *vacA* s1 genotype strains, which enhanced gastric mucosal inflammation, are significantly higher than those with *cagA*-negative and *vacA* s2 genotype strains.¹⁷ The relationship between the success/failure of *H. pylori* eradication therapy and virulence factors has been explained by the enhanced gastric mucosal inflammation, resulting in a higher level of inflammatory cytokines. Good correlation between *cagA* positivity and severe gastric inflammation has been confirmed.^{71,72} The *cagA*-positive strains produce significantly higher *IL-1β* in gastric mucosa compared with that of *cagA*-negative strains.^{23,24} Therefore, the cure rate in *cagA* status and *vacA* s1 type is considered to be influenced via different cytokine levels in the gastric mucosa, the same as cytokine gene polymorphisms.

VI. Association with CYP2C19 genotype and cytokine polymorphism

The genotypes of CYP2C19 and *IL-1B*-511 are independent factors for *H. pylori* eradication therapy. Therefore, patients with CYP2C19 RM and *IL-1B*-511 C/C genotype are considered to have lower bioavailability of a PPI, as well as a higher potential gastric acid secretion, resulting in the insufficient acid inhibition by a PPI at the standard dose during the eradication therapy. Moreover, in combined analysis of both genotypes of CYP2C19 and *IL-1B*-511, additive effects for eradication are also being considered.

IL-1B-511 genotype-dependent differences in the cure rates of *H. pylori* infection are observed only in patients with RM of CYP2C19, but not in those with IM or PM genotype status (Table 2).^{31,32} In combined analysis of previous reports, the eradication rate is 52% (51/98, 95%CI: 42–62%) for the *IL-1B*-511 C/C genotype in CYP2C19 RM, which is lower than the *IL-1B*-511 C/T and T/T genotype (80%, 185/231, 95%CI: 74–85%) (Table 3). Similarly, CYP2C19 genotype-dependent differences in the cure rates of *H. pylori* infection are observed in patients with the *IL-1B*-511 C/C genotype.^{30–32} Take *et al.* also reported that in the *IL-1B*-511 C/T and T/T group there was no statistically significant difference in the

cure rate among the three CYP2C19 genotype subgroups. However, in the *IL-1B-511 C/C* group the cure rate among CYP2C19 PM patients (93.3%) was significantly higher than among the CYP2C19 RM (60.0%) and IM patients (63.6%).³⁰ CYP2C19 RM in the *IL-1B-511 C/C* genotype has an eradication rate of 52%, which is lower than that in the CYP2C19 IM (83%, 110/132, 95%CI: 76–89%) and PM genotype (97%, 31/32, 95%CI: 84–100%) (Table 3). The OR of the CYP2C19 IM-*IL-1B-511 C/C* type, CYP2C19 RM-*IL-1B-511 T/C* and *T/T* type and the CYP2C19 RM-*IL-1B-511 C/C* type are 2.43, 3.00 and 11.15, respectively, which significantly increases compared with that of CYP2C19 PM-*IL-1B-511 T/C* and *T/T* types (Table 3).

Therefore, patients with such combined genotypes (i.e. RM of *CYP2C19* plus *IL-1B-511 C/C*) will require another advanced treatment for a sufficient acid inhibition throughout a 24-hour period, such as treatment with a more frequent PPI dosing (e.g. RPZ 10 mg 4-times-daily)^{62,63,73} and concomitant therapy of PPI and H2RA.⁷⁴

VII. Conclusion

We have reviewed *H. pylori* eradication therapy mainly in relation to the inflammatory cytokine and its polymorphism. There are many genetic factors associated with therapeutic outcomes of *H. pylori* eradication therapy with a PPI and antimicrobial agents. We would like to recommend the tailored regimens based on the genetic inflammatory cytokine polymorphism the same as relevant pharmacogenomics and microbiological factors (e.g. antibiotic resistance and *H. pylori* virulent factors).¹⁸ However, because the two major factors, antibiotics resistance and CYP2C19 RM, potentially influence the success/failure of eradication compared with the genetic inflammatory cytokine polymorphisms, we are not sure that all factors should be determined before the treatment. Moreover, there is genetic variation of cytokine genotypes among different populations, and it is unclear whether this evidence, that the cure rate of eradication is influenced by inflammatory cytokine polymorphisms, is adapted to both the Asian population and Western populations. Therefore, advanced data to evaluate above the hypothesis will be required.

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Abbreviations

AMPC	amoxicillin
CAM	clarithromycin
<i>H. pylori</i>	<i>Helicobacter pylori</i>
IM	intermediate metabolizer
LPZ	lansoprazole
OPZ	omeprazole
PM	poor metabolizer
RM	rapid metabolizer
RPZ	rabeprazole

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Figure 1.

The (a) 24-hour pH-profile and the (b) median 24-hour pH in the patients with success and failure in *Helicobacter pylori* (*H. pylori*) eradication.²⁰ In patients with successful cure of *H. pylori* infection, the median 24-hour pH is significantly higher than that in patients with therapeutic failure (a,b). —○— Success; —■— Failure.

Figure 2.

The association with 24-hour pH and percent times of pH < 4.0 during the 24-hour dosing period.²⁰ The majority of patients can eradicate *Helicobacter pylori* (*H. pylori*) infection with a triple therapy, when the percent time of pH < 4.0 during the 24-hour post-dose period is less than 10% and the 24-hour pH is higher than 6.0 (shaded area). On the other hand, when the percent time of pH < 4.0 is longer than 40% or when the 24-hour pH is lower than 4.4 during treatment (dotted area), the eradication with a triple therapy appears to be quite difficult. ○ Success/clarithromycin (CAM)-sensitive or unknown; ▽ Success/CAM-resistant; × Failure/CAM-sensitive; ▼ Failure/CAM-resistant or unknown.

Figure 3. The association with *IL-1B-511* polymorphisms and the eradication rates for *Helicobacter pylori* infection. The eradication rate in *IL-1B-511* C/T and T/T genotypes is significantly higher than that in the C/C genotype.

Table 1
The association with the success rate of *Helicobacter pylori* eradication therapy and cytokine polymorphisms

Authors	Year	Number	Regimen	Gene	Genotype	OR	95%CI
Take ³⁰	2003	231	OAC, LAC, RAC	<i>IL-1B</i> -511	CT, TT	138/172 (80%)	1.00
					CC	47/59 (80%)	1.04 0.50–2.17
Furuta ³¹	2004	336	OAC, LAC	<i>IL-1B</i> -511	TT	71/75 (95%)	1.00
					CT	147/164 (90%)	2.05 0.67–6.33
					CC	75/97 (77%)	5.21 1.71–15.86
Sugimoto ³²	2006	360	OAC, LAC, RAC	<i>IL-1B</i> -511	TT	67/76 (88%)	1.00
				CT	164/187 (88%)	1.04	0.46–2.38
					CC	70/97 (72%)	2.31 1.00–5.35
				<i>IL-1RN</i>	*2 carrier	28/37 (76%)	1.00
					Non-*2	273/323 (85%)	0.52 0.23–1.17
				<i>TNF-A</i> -857	T carrier	94/115 (82%)	1.00
					CC	207/245 (84%)	0.72 0.40–1.31
				<i>TNF-A</i> -863	A carrier	99/117 (85%)	1.00
					CC	202/243 (83%)	0.99 0.54–1.82
				<i>TNF-A</i> -1031	C carrier	99/118 (84%)	1.00
					TT	202/242 (83%)	0.91 0.50–1.67
				<i>IL-10</i> -1082	G carrier	65/76 (86%)	1.00
					AA	236/284 (83%)	1.08 0.53–2.22
				<i>IL-10</i> -819	C carrier	156/181 (85%)	1.00
					TT	145/179 (81%)	1.26 0.71–2.24
				<i>IL-10</i> -592	C carrier	145/167 (87%)	1.00
					AA	156/193 (81%)	1.36 0.76–2.44
				<i>IL-1B</i> -31	CC	14/14 (100%)	1.00
					CT	30/36 (83%)	NA –
					TT	13/17 (77%)	NA –
				<i>TNF-A</i> -1031	CC	2/2 (100%)	1.00
					T carrier	55/65 (80%)	NA –
Ishida ⁶⁸	2006	67	LAC				
Zambon ³³	2007	102	OAC	<i>IL-10</i> -1082/-892/-592	ATA/ATA	8/9 (89%)	1.00

Authors	Year	Number	Regimen	Gene	Genotype	OR	95%CI
					Non-ATA/ATA	49/93 (51%)	7.18 0.86–59.76

Although Zambon *et al.*³³ performed *IL-1B*-31, *IL-1RN*, *IFN-γ*+874, *TNF-A*-238, -308, -376, -857, -1031, *IL-12A*+6686 and *IL-12B*+15485 genotyping, there were no detail data.

CI, confidence interval; IL, interleukin; LAC, lansoprazole, amoxicillin and clarithromycin; NA, no analysis; OAC, omeprazole, amoxicillin and clarithromycin; OR, odds ratio; RAC, rabeprazole, amoxicillin and clarithromycin; TNF, tumor necrosis factor.

Table 2

The association with *IL-1B-511* polymorphism and CYP2C19 genotypes for *Helicobacter pylori* eradication therapy

Authors	Number	<i>IL-1B-511</i>	CYP2C19	RM	IM	PM
Take ³⁰	231	C/T, T/T	44/61 (72%)	72/92 (78%)	22/28 (79%)	
		C/C	12/20 (60%)	21/33 (64%)	14/15 (93%)*	
Furuta ³¹	336	T/T	20/22 (91%)**	36/37 (97%)	31/32 (97%)	
		C/T	44/56 (79%)**	77/82 (94%)	26/26 (100%)	
		C/C	17/35 (49%)	49/53 (92%)*	9/9 (100%)*	
Sugimoto ³²	360	T/T	27/33 (82%)**	26/27 (96%)	14/16 (88%)	
		C/T	50/59 (85%)**	86/99 (87%)	28/29 (97%)	
		C/C	22/43 (51%)*	40/46 (87%)*	8/8 (100%)*	

* $P < 0.05$ compared with RM genotype of CYP2C19 and

** $P < 0.05$ compared with *IL-1B-511* C/C genotype.

Studies of Ishida *et al.*⁶⁸ and Zambon *et al.*³³ had no raw data of combined analysis of CYP2C19 and *IL-1B-511* (or *IL-1B-31*) genotype status. IM, intermediate metabolizer; PM, poor metabolizer; RM, rapid metabolizer.

Table 3

The odds risk for eradication failure of *Helicobacter pylori* infection

CYP2C19	IL-1B-511	Number	Cure rate	OR	95%CI	P-value
PM	T/T and T/C	131	92.4%	1.00		
	C/C	32	96.9%	0.39	0.05–3.17	0.38
IM	T/T and T/C	337	88.1%	1.63	0.79–3.36	0.18
	C/C	132	83.3%	2.42	1.10–5.34	0.03
RM	T/T and T/C	231	80.1%	3.00	1.46–6.19	<0.01
	C/C	98	52.0%	11.15	5.23–23.78	<0.01

CI, confidence interval; IM, intermediate metabolizer; OR, odds ratio; PM, poor metabolizer; RM, rapid metabolizer.