

Elevated Serum anti-*Helicobacter pylori* IgG Levels is a Predictor of Successful Eradication Therapy

Satoshi Shinozaki, Hirotsugu Sakamoto, Yoshikazu Hayashi, Kenjiro Shinozaki, Alan Kawarai Lefor, Hironori Yamamoto

Satoshi Shinozaki, Shinozaki Medical Clinic, Utsunomiya, 321-3223, Japan, and Division of Gastroenterology, Department of Medicine, Jichi Medical University, Shimotsuke, 329-0498, Japan
Hirotsugu Sakamoto, Yoshikazu Hayashi, Hironori Yamamoto, Division of Gastroenterology, Department of Medicine, Jichi Medical University, Shimotsuke, 329-0498, Japan

Kenjiro Shinozaki, Shinozaki Medical Clinic, Utsunomiya, 321-3223, Japan

Alan Kawarai Lefor, Department of Surgery, Jichi Medical University, 329-0498, Japan

Correspondence to: Hironori Yamamoto, MD, Division of Gastroenterology, Department of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498, Japan.

Email: ireef@jichi.ac.jp

Telephone: +81-285-58-7347

Fax: +81-285-40-6598

Received: August 28, 2015

Revised: October 3, 2015

Accepted: October 6, 2015

Published online: October 21, 2015

ABSTRACT

AIM: To identify a predictor of successful primary *Helicobacter pylori* (*H. pylori*) eradication assessed in routine clinical practice.

METHODS: From February 2013 to January 2015, 186 patients underwent primary eradication therapy. We retrospectively reviewed the medical records. All patients underwent EGD before eradication therapy and *H. pylori* infection was diagnosed by ≥ 10 U/mL serum anti-*H. pylori* IgG. We used standard triple therapy including a proton pump inhibitor (PPI) (rabeprazole 10 mg or lansoprazole 30 mg), clarithromycin 200 mg and amoxicillin 750 mg twice daily for seven days. To determine if eradication succeeded, a ^{13}C -urea breath test was performed on all patients more than eight weeks after primary eradication.

RESULTS: The overall success rate of *H. pylori* eradication therapy was 62% (116/186). We assessed potential predictors of successful primary *H. pylori* eradication therapy including gender, age, smoking

habits, prior PPI intake, kind of PPI, serum IgG value and degree of atrophy. Univariate analysis showed that high serum IgG significantly predicts successful eradication (odds ratio (OR) 2.583, 95% confidence interval (CI) 1.285-5.191, $p=0.008$). The eradication rate was 77% (43/56) in the ≥ 45 U/mL group and 56% (73/130) in the < 45 U/mL group, and significance was confirmed by multivariate analysis (OR 2.626, 95% CI 1.269-5.436, $p=0.009$). Multivariate analysis showed a trend that advanced age (≥ 70 year-old) increased the rate of successful eradication (OR 1.669, 95% CI 0.857-3.252, $p=0.132$).

CONCLUSION: Elevated serum IgG significantly predicts successful primary *H. pylori* eradication.

© 2015 ACT. All rights reserved.

Key words: *Helicobacter pylori*; IgG; Treatment response; Proton pump inhibitor; Antibiotics

Shinozaki S, Sakamoto H, Hayashi Y, Shinozaki K, Lefor AK, Yamamoto H. Elevated Serum anti-*Helicobacter pylori* IgG Levels is a Predictor of Successful Eradication Therapy. *Journal of Gastroenterology and Hepatology Research* 2015; 4(10): 1797-1800 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1362>

INTRODUCTION

Helicobacter pylori (*H. pylori*) eradication is the standard treatment for preventing gastric ulcers and cancer throughout the world. In Japan, *H. pylori* eradication therapy for *H. pylori* gastritis has been approved by the National Health Insurance system since February 2013. For primary eradication therapy, triple drug therapy including a proton pump inhibitor (PPI), clarithromycin and amoxicillin for one week is the approved regimen. Despite more patients undergoing this eradication regimen in Japan, the success rate of primary *H. pylori* eradication has been decreasing over the last decade because of emerging antibiotic resistance^[1].

Factors which predict successful *H. pylori* eradication therapy have been reported, including the absence of antibiotic resistance^[2], poor metabolism of PPI due to CYP2C19 polymorphism^[3,4], and positive cytotoxin-associated gene A (cagA) status^[5]. These factors are generally not evaluated in routine clinical practice, but require a research setting. The aim of this study is to identify a factor that predicts successful primary *H. pylori* eradication therapy that can be easily assessed in routine clinical practice.

METHODS

Study population

From February 2013 to January 2015, 214 patients underwent primary *H. pylori* eradication triple therapy at our institution. Twenty-eight patients were excluded for the following reasons: six patients had undergone distal gastrectomy, 15 patients were not diagnosed with an *H. pylori* infection by serum IgG and seven patients did not visit the clinic after eradication therapy. The remaining 186 patients comprise the study group. The diagnosis of *H. pylori* infection was defined as a serum IgG level ≥ 10 U/mL using an enzyme immunoassay kit (E Plate®, EIKEN CHEMICAL CO.,LTD., Tokyo, Japan). We retrospectively reviewed patient medical records and collected the following data: gender, age, smoking habits, prior PPI use, adverse events, laboratory findings and endoscopic findings. Prior PPI administration was defined as at least one week of PPI use prior to undergoing primary eradication. Esophagogastroduodenoscopy was performed on all patients, and atrophic changes were classified based on the Kimura-Takemoto classification^[6]. When esophagogastroduodenoscopy showed both obvious atrophy and negative *H. pylori* serology, we performed other screening tests. The Institutional Review Board approved this study.

Protocol for primary *H. pylori* eradication therapy

The protocol for primary *H. pylori* eradication included standard triple therapy with a PPI (rabeprazole 10 mg or lansoprazole 30 mg), clarithromycin 200 mg and amoxicillin 750 mg twice daily for seven days. The PPI choice was made by the physician in charge. To determine whether primary *H. pylori* eradication succeeded or not, a ¹³C-urea breath test (UBT) using Ubit® (Otsuka Pharmaceuticals, Tokyo, Japan) was performed on all patients more than eight weeks after primary eradication, with a cut-off value of 2.5‰. Prior to the UBT, PPI administration was discontinued for at least two weeks if the patient was continuously receiving the PPI. Successful primary *H. pylori* eradication therapy was defined as a negative UBT.

Statistical analysis

Data was analyzed with StatFlex ver. 6.0 software (Artech Co., Ltd. Osaka, Japan). Statistical analysis was performed using Chi-Squared test for univariate analysis and multiple logistic regression analysis for multivariate analysis.

RESULTS

Clinical characteristics of 186 patients

Demographic data and endoscopic findings of the 186 patients are shown in Table 1. About one-third of the patients underwent routine PPI administration. Endoscopically, all patients had gastric atrophy and most patients had open-type atrophy. Adverse events including diarrhea and/or a bitter taste occurred in 16 patients (9%).

Predictive factors for successful primary *H. pylori* eradication therapy

The overall success rate of *H. pylori* eradication therapy was 62% (116/186). We assessed potential predictors of successful primary *H. pylori* eradication therapy including gender, age, smoking habits, prior PPI intake, kind of PPI, serum IgG value and degree of atrophy (Table 2). Univariate analysis showed that high serum IgG was a significant predictor of successful eradication (odds ratio (OR) 2.583, 95% confidence interval (CI) 1.285-5.191, $p=0.008$). The eradication rate was 77% (43/56) in the ≥ 45 U/ml group and 56% (73/130) in the < 45 U/mL group, and significance was confirmed by multivariate analysis (OR 2.626, 95% CI 1.269-5.436, $p=0.009$). Multivariate analysis also showed that advanced age (≥ 70 years) increased the success rate (OR 1.669, 95% CI 0.857-3.252, $p=0.132$), although this did not attain statistical significance. It is notable that about half of the patients with IgG ≤ 20 U/mL had eradication (52%, 23/44), while all patients with IgG ≥ 100 U/mL had eradication (100%, 6/6).

Table 1 Clinical characteristics of 186 patients.

	N (%)
Gender, male	73 (39%)
Age, mean (range)	65.2 (28 - 87)
Current smoker	19 (10%)
Prior PPI administration	64 (34%)
Kind of PPI (rabeprazole/lansoprazole)	50 (27%) / 136 (73%)
Serum HPIgG (<45/ ≥ 45)	130 (70%) / 56 (30%)
Endoscopic findings	
Atrophic gastritis (closed type/open type)	30 (16%) / 156 (84%)
Gastric ulcer or scar	11 (6%)
Duodenal ulcer or scar	13 (7%)
Gastric hyperplastic polyp	25 (13%)

Table 2 Univariate and multivariate analyses of factors affecting success of primary HP eradication therapy.

Factor	Eradication rate, % (n)	Univariate analysis			Multivariate analysis			
		Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value	
Gender	Male	67% (49/73)	1.402	0.758-2.592	0.282	1.333	0.694-2.562	0.389
	Female	59% (67/113)						
Age	≥ 70 y	69% (46/67)	1.533	0.816-2.880	0.184	1.669	0.857-3.252	0.132
	< 70 y	59% (70/119)						
Current smoking	Present	74% (14/19)	1.784	0.621-5.129	0.283	1.857	0.587-5.881	0.292
	Absent	61% (102/167)						
Prior PPI intake	Present	59% (38/64)	0.824	0.443-1.533	0.542	0.893	0.460-1.733	0.737
	Absent	64% (78/122)						
Kind of PPI	Rabeprazole	66% (33/50)	1.240	0.629-2.443	0.535	1.108	0.539-2.278	0.780
	Lansoprazole	61% (83/136)						
Serum IgG	≥ 45 U/ml	77% (43/56)	2.583	1.285-5.191	0.008	2.626	1.269-5.436	0.009
	< 45 U/ml	56% (73/130)						
Degree of atrophy	Open type	63% (99/156)	1.328	0.602-2.928	0.482	1.067	0.463-2.460	0.878
	Closed type	57% (17/30)						

DISCUSSION

We clarified a statistically significant predictor of successful primary *H. pylori* eradication therapy in the present study. Serum IgG can be measured by a simple blood test in routine clinical practice. There have been several reports regarding a predictor of successful primary *H. pylori* eradication therapy^[2,3,5,7,8]. However, most of the previously reported predictors involve measurements that are not evaluated in routine clinical practice. To our knowledge, this is the first report to show a relationship between primary *H. pylori* eradication rate and the serum IgG level.

In the human immune system, IgG plays important roles including binding pathogens, opsonization and activation of the complement system, which result in bacterial elimination. The serum IgG level is a reliable test to confirm *H. pylori* infection having 98% sensitivity^[9]. This test has some advantages including: (1) cost-effectiveness; (2) easy and quick to perform with a blood sample; (3) it does not require endoscopy or biopsy; and (4) it does not require discontinuation of acid suppressing medications. However, it is not recommended to determine *H. pylori* infection status after eradication therapy. Past studies of IgG levels focused on changes in post-eradication IgG levels^[10-12]. More than a 25% decrement six months after eradication treatment is considered a reliable marker for eradication^[12].

We first investigated using serum IgG level as a predictive factor for successful eradication. The serum IgG level is considered to be an indicator of immune status for specific pathogens, and reflects bacterial proliferation and activity. Suzuki *et al* reported that a *cagA* positive status reflects the high proliferative rate of *H. pylori* with an increased success rate for primary *H. pylori* eradication^[5]. Generally, more proliferative bacteria are more sensitive to antibiotics. Hence, patients with high serum IgG levels may be especially sensitive to antibiotics. Malm *et al* reported that patients with a high serum IgG titer can block norovirus infections^[13]. Additionally, the effects of vaccination are assessed using serum IgG levels in various infectious diseases. We suspect that patients with high serum IgG levels are ready to mount an immune response to *H. pylori* and are thus less tolerant of *H. pylori*. A co-operative effect of antibiotic susceptibility and high humoral immunity may facilitate *H. pylori* eradication therapy. Eventually, patients with high serum IgG levels show a good result from *H. pylori* eradication therapy. Serum IgG levels achieved by an infection might reflect not only the severity of the infection but also the reactivity of the host immune system. Further studies are needed to determine the relationship between degree of inflammation based on the pathological specimen and serum IgG level.

Although other reliable predictive factors for successful *H. pylori* eradication have been reported, *cagA* status or antibiotic resistance cannot be evaluated in routine clinical practice. Serum IgG levels can be assessed by a simple blood test without endoscopy, biopsy or other special procedures. Since *cagA*-positive *H. pylori* status and high serum IgG levels reflect a high growth rate of *H. pylori*, *H. pylori* eradication in such patients may show high antibiotic susceptibility and a high suppressive effect against future gastric cancer. In this study, advanced age showed a trend toward a higher eradication rate, and a large French study reported advanced age as a significant factor for successful eradication^[14]. Gastric pH elevation increases the rate of successful eradication^[15]. Although it has been reported that integrated acidity in the general population is not affected by age^[16], acidity in the elderly may be more suppressed by PPI than in younger people. Despite the small number of patients, this study implies a dose-dependent relationship between the IgG level and eradication rate since the >100 IgG group had a 100%

(6/6) eradication rate, and the <20 IgG group had only a 52% (23/44) eradication rate. To clarify these trends, further large studies are necessary.

A particular strength of this study is the homogeneity of the diagnosis and treatment regimens. There are various eradication regimens used worldwide^[17]. We used the same the dose of antibiotics for the same duration (seven days) in all patients. Further, all patients were diagnosed by serum IgG levels before eradication. Eradication of *H. pylori* was confirmed by a negative UBT. Therefore, the analysis of predictive factors in this study is more reliable than other large studies involving various regimens and/or treatment durations. Although a negative UBT can also include false positives^[18], these patients were evaluated in the same condition and we did not wait for a second eradication because delayed second eradication increases eradication failure^[19]. The overall success rate of primary *H. pylori* eradication therapy in the present study is 62%, which is relatively low compared with large studies from other countries^[5,20], but similar to another large Japanese study^[21]. Stringent policies for the use of antibiotics have not been distributed in Japan. A recent large Japanese study reported 36% clarithromycin resistance^[22], which may impact this low eradication rate.

We recognize some limitations to this study including: (1) CYP2C19 polymorphism was not evaluated. A low eradication rate was reported with this rapid metabolizer^[3]; (2) Clarithromycin resistance was not assessed; (3) this is a single center, retrospective study; and (4) *cagA* status was not evaluated in this study. Fujiya *et al* reported that the rate of *cagA*-positive *H. pylori* is 73% in Japan^[23].

In conclusion, a high serum IgG level is a significant predictor of successful primary *H. pylori* eradication therapy. The high proliferative rate of *H. pylori* and host recognition may enhance eradication by antibiotics.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

- 1 Sasaki M, Ogasawara N, Utsumi K, Kawamura N, Kamiya T, Kataoka H, Tanida S, Mizoshita T, Kasugai K, Joh T. Changes in 12-Year First-Line Eradication Rate of *Helicobacter pylori* Based on Triple Therapy with Proton Pump Inhibitor, Amoxicillin and Clarithromycin. *J Clin Biochem Nutr* 2010; **47**(1): 53-58 [PMID: 20664731 PMID: PMC2901764 DOI: 10.3164/jcbs.10-10]
- 2 Houben MH, van de Beek D, Hensen EF, de Craen AJ, Rauws EA, Tytgat GN. A systematic review of *Helicobacter pylori* eradication therapy--the impact of antimicrobial resistance on eradication rates. *Aliment Pharmacol Ther* 1999; **13**(8): 1047-1055 [PMID: 10468680]
- 3 Furuta T, Ohashi K, Kamata T, Takashima M, Kosuge K, Kawasaki T, Hanai H, Kubota T, Ishizaki T, Kaneko E. Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med* 1998; **129**(12): 1027-1030 [PMID: 9867757]
- 4 Tang HL, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of *H. pylori* infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS One* 2013; **8**(4): e62162 [PMID: 23646118 PMID: PMC3639978 DOI: 10.1371/journal.pone.0062162]
- 5 Suzuki T, Matsuo K, Sawaki A, Ito H, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, Tajima K. Systematic review and meta-analysis: importance of *CagA* status for successful eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*

- 2006; **24**(2): 273-280 [PMID: 16842453 DOI: 10.1111/j.1365-2036.2006.02994.x]
- 6 Kimura K, Takemoto T. An Endoscopic Recognition of the Atrophic Border and its Significance in Chronic Gastritis. *Endoscopy* 1969; **1**(3): 87-97 [DOI: 10.1055/s-0028-1098086]
 - 7 Suzuki T, Matsuo K, Ito H, Sawaki A, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, Tajima K. Smoking increases the treatment failure for *Helicobacter pylori* eradication. *Am J Med* 2006; **119**(3): 217-224 [PMID: 16490464 DOI: 10.1016/j.amjmed.2005.10.003]
 - 8 van Doorn LJ, Schneeberger PM, Nouhan N, Plaisier AP, Quint WG, de Boer WA. Importance of *Helicobacter pylori* cagA and vacA status for the efficacy of antibiotic treatment. *Gut* 2000; **46**(3): 321-326 [PMID: 10673291 PMID: PMC1727836]
 - 9 Thijs JC, van Zwet AA, Thijs WJ, Oey HB, Karrenbeld A, Stellaard F, Luijck DS, Meyer BC, Kleibeuker JH. Diagnostic tests for *Helicobacter pylori*: a prospective evaluation of their accuracy, without selecting a single test as the gold standard. *Am J Gastroenterol* 1996; **91**(10): 2125-2129 [PMID: 8855734]
 - 10 Morris AJ, Ali MR, Nicholson GI, Perez-Perez GI, Blaser MJ. Long-Term Follow-up of Voluntary Ingestion of *Helicobacter pylori*. *Ann Intern Med* 1991; **114**(8): 662-663 [DOI: 10.7326/0003-4819-114-8-662]
 - 11 Wang D, Chiu T, Chiu KW. Clinical implication of immunoglobulin G levels in the management of patients with *Helicobacter pylori* infection. *J Am Board Fam Med* 2014; **27**(5): 682-689 [PMID: 25201937 DOI: 10.3122/jabfm.2014.05.130181]
 - 12 Marchildon P, Balaban DH, Sue M, Charles C, Doobay R, Passaretti N, Peacock J, Marshall BJ, Peura DA. Usefulness of serological IgG antibody determinations for confirming eradication of *Helicobacter pylori* infection. *Am J Gastroenterol* 1999; **94**(8): 2105-2108 [PMID: 10445535 DOI: 10.1111/j.1572-0241.1999.01285.x]
 - 13 Malm M, Uusi-Kerttula H, Vesikari T, Blazevic V. High serum levels of norovirus genotype-specific blocking antibodies correlate with protection from infection in children. *J Infect Dis* 2014; **210**(11): 1755-1762 [PMID: 24970849 DOI: 10.1093/infdis/jiu361]
 - 14 Broutet N, Tchamgoue S, Pereira E, Lamouliatte H, Salamon R, Megraud F. Risk factors for failure of *Helicobacter pylori* therapy—results of an individual data analysis of 2751 patients. *Aliment Pharmacol Ther* 2003; **17**(1): 99-109 [PMID: 12492738]
 - 15 Sugimoto M, Furuta T, Shirai N, Kodaira C, Nishino M, Ikuma M, Ishizaki T, Hishida A. Evidence that the degree and duration of acid suppression are related to *Helicobacter pylori* eradication by triple therapy. *Helicobacter* 2007; **12**(4): 317-323 [PMID: 17669104 DOI: 10.1111/j.1523-5378.2007.00508.x]
 - 16 Shih GL, Brensinger C, Katzka DA, Metz DC. Influence of age and gender on gastric acid secretion as estimated by integrated acidity in patients referred for 24-hour ambulatory pH monitoring. *Am J Gastroenterol* 2003; **98**(8): 1713-1718 [PMID: 12907323 DOI: 10.1111/j.1572-0241.2003.07586.x]
 - 17 Papastergiou V, Georgopoulos SD, Karatapanis S. Treatment of *Helicobacter pylori* infection: Past, present and future. *World J Gastrointest Pathophysiol* 2014; **5**(4): 392-399 [PMID: 25400982 PMID: PMC4231503 DOI: 10.4291/wjgp.v5.i4.392]
 - 18 Kwon YH, Kim N, Lee JY, Choi YJ, Yoon K, Hwang JJ, Lee HJ, Lee A, Jeong YS, Oh S, Yoon H, Shin CM, Park YS, Lee DH. The Diagnostic Validity of Citric Acid-Free, High Dose (13) C-Urea Breath Test After *Helicobacter pylori* Eradication in Korea. *Helicobacter* 2015; **20**(3): 159-168 [PMID: 25640474 DOI: 10.1111/hel.12189]
 - 19 Nishizawa T, Suzuki H, Takahashi M, Suzuki M, Hibi T. Delay of second-line eradication therapy for *Helicobacter pylori* can increase eradication failure. *J Gastroenterol Hepatol* 2013; **28**(10): 1608-1610 [PMID: 23701705 DOI: 10.1111/jgh.12281]
 - 20 McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2012; **36**(5): 414-425 [PMID: 22803691 DOI: 10.1111/j.1365-2036.2012.05211.x]
 - 21 Kawai T, Takahashi S, Suzuki H, Sasaki H, Nagahara A, Asaoka D, Matsuhisa T, Masaoaka T, Nishizawa T, Suzuki M, Ito M, Kurihara N, Omata F, Mizuno S, Torii A, Kawakami K, Ohkusa T, Tokunaga K, Mine T, Sakaki N. Changes in the first line *Helicobacter pylori* eradication rates using the triple therapy—a multicenter study in the Tokyo metropolitan area (Tokyo *Helicobacter pylori* study group). *J Gastroenterol Hepatol* 2014; **29** Suppl 4: 29-32 [PMID: 25521730 DOI: 10.1111/jgh.12796]
 - 22 Nishizawa T, Maekawa T, Watanabe N, Harada N, Hosoda Y, Yoshinaga M, Yoshio T, Ohta H, Inoue S, Toyokawa T, Yamashita H, Saito H, Kuwai T, Katayama S, Masuda E, Miyabayashi H, Kimura T, Nishizawa Y, Takahashi M, Suzuki H. Clarithromycin Versus Metronidazole as First-line *Helicobacter pylori* Eradication: A Multicenter, Prospective, Randomized Controlled Study in Japan. *J Clin Gastroenterol* 2014 [PMID: 24921211 DOI: 10.1097/mcg.000000000000165]
 - 23 Fujiya K, Nagata N, Uchida T, Kobayakawa M, Asayama N, Akiyama J, Shimbo T, Igari T, Banerjee R, Nageshwar Reddy D, Mizokami M, Uemura N. Different gastric mucosa and CagA status of patients in India and Japan infected with *Helicobacter pylori*. *Dig Dis Sci* 2014; **59**(3): 631-637 [PMID: 24282059 DOI: 10.1007/s10620-013-2961-x]
- Peer reviewer:** Osamu Handa, Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, 465 Kajicho, Kawaramachi-Hirokoji, Kamigyo, Kyoto. 602-8566, JAPAN.