

Effect of *Helicobacter pylori* eradication in the treatment of Japanese patients with chronic idiopathic urticaria

SHINSAKU FUKUDA¹, TADASHI SHIMOYAMA¹, NORIKO UMEGAKI², TATSUYA MIKAMI¹, HAJIME NAKANO²,
and AKIHIRO MUNAKATA¹

¹First Department of Internal Medicine, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki 036-8562, Japan

²Department of Dermatology, Hirosaki University School of Medicine, Hirosaki, Japan

Background. Infection with *Helicobacter pylori* has been associated with chronic idiopathic urticaria (CIU). The aim of this study was to investigate the efficacy of *H. pylori* eradication in the treatment of patients with CIU. **Methods.** Fifty patients with CIU (16 men and 34 women; age 25–75 years) and 100 sex- and age-matched control subjects were enrolled in the study. Presence of IgG antibody to *H. pylori* was examined by serology. *H. pylori*-seropositive patients with CIU received endoscopy to confirm *H. pylori* infection. Patients infected with *H. pylori* received eradication therapy comprising lansoprazole, amoxicillin, and either clarithromycin or metronidazole. At least 2 months after finishing the eradication therapy, a ¹³C-urea breath test was performed, and the effect of eradication therapy on the CIU was scored, using a three-point scale, as complete remission, partial remission, or no improvement. **Results.** In the 50 patients with CIU, 26 (52%) were *H. pylori*-seropositive, while 48% (48/100) of the control subjects were seropositive (statistically not significant). Nineteen out of the 26 patients with CIU infected with *H. pylori* received eradication therapy, and eradication was successful in 17 patients. In the 17 *H. pylori*-eradicated patients, 6 (35%) had complete remission and 11 (65%) had complete remission or partial remission. On the other hand, in the 9 patients without *H. pylori* eradication, only 2 (22%) showed partial remission and 7 (78%) had no improvement. **Conclusions.** Eradication of *H. pylori* would be a valid choice for patients with CIU, although the prevalence of *H. pylori* infection is not higher in patients with CIU than it is in controls.

Key words: *Helicobacter pylori*, chronic urticaria

Introduction

Helicobacter pylori, a gram-negative bacterium, colonizes the gastric mucosa and induces acute gastritis, which later develops into chronic active gastritis. Infection with *H. pylori* is recognized as a causative factor for peptic ulcer diseases and also increases the risk for the development of gastric cancer.¹ Eradication of *H. pylori* has been performed safely and effectively for the treatment of several gastrointestinal diseases.

The use of antibiotics to cure underlying focal infections has shown therapeutic effects in several diseases, such as chronic idiopathic urticaria (CIU) and Henoch-Schönlein disease. The gastrointestinal tract is recognized as a site of focal infections, and *H. pylori* infection in the stomach is the most common persistent infection in humans. Thus, in recent years, the effect of eradication of *H. pylori* has been investigated for the treatment of extra-digestive diseases, including CIU. Several studies have shown a high prevalence of *H. pylori* infection in CIU,² and regression of cutaneous signs and symptoms has been shown by eradication of *H. pylori*.^{2–5} However, there are also a number of studies that failed to find an association between *H. pylori* infection and CIU.^{6–8} This controversy is possibly associated with differences in methods of eradication (duration and antibiotics) and in the studied populations. To date, in Japan, only a few studies have examined the therapeutic effects of eradication of *H. pylori* for CIU.^{9,10} Furthermore, in these studies, eradication was not performed by Japanese standard triple therapy in many cases.

H. pylori is highly diverse genetically, and several genotypes have been associated with severe gastric mucosal inflammation. Possession of the *cagA* gene is the most well-known virulent phenotype at present. However, associations between genotypes of *H. pylori*, including *cagA*, and CIU have not been examined.

The aims of this study were to examine the prevalence of *H. pylori* infection in Japanese patients with

CIU and to investigate the effect of the Japanese standard *H. pylori* eradication regimen for the treatment of CIU. We also studied the prevalence of the *cagA* gene in *H. pylori* strains isolated from patients with CIU.

Patients, materials, and methods

During August 2000 and December 2002, 50 patients (16 men and 34 women; mean age, 48.2 years; range, 25–75 years) affected by CIU were enrolled in the study. The enrolled patients came from a series of consecutive patients referred to the Dermatology Department of Hirosaki University Hospital. Serum samples were collected from all the patients to examine for the presence of IgG antibody to *H. pylori* (E plate; Eiken, Tokyo, Japan). Sera were also obtained from subjects who were endoscopically diagnosed as normal, or who had chronic gastritis, to study the prevalence of IgG antibody to *H. pylori* in a control population. For each patient with CIU, 2 sex- and age-matched subjects (32 men and 68 women; mean age, 48.3 years; range, 24–76 years) were examined as control subjects. Patients and control subjects were excluded if they had received antibiotics within 2 months prior to the examination. All subjects provided their written informed consent before entering the study. This study was approved by the Ethics Committee of Hirosaki University.

H. pylori-seropositive patients with CIU underwent upper gastrointestinal endoscopy to confirm *H. pylori* infection by at least one method; histology, rapid urease test, and bacterial culture. Twenty-six patients were determined to have *H. pylori* infection and 21 of them received eradication therapy, comprising 1 week of lansoprazole (LPZ; 30 mg b.d.), amoxicillin (AMOX; 750 mg b.d.), and clarithromycin (CLA; 200 mg b.d.) as the first-line therapy. If *H. pylori* was not eradicated by the first-line therapy, the patients received second-line therapy, comprising LPZ (30 mg b.d.), AMOX (750 mg b.d.), and metronidazole (MNZ; 250 mg b.d.) for 1 week. A ^{13}C -urea breath test (UBT) was performed at least 6 weeks after the finishing of each treatment to examine treatment results. Proton-pump inhibitors (PPIs) and other antiulcer agents that may affect *H. pylori* urease activity were not used after the patients finished the treatment prior to the ^{13}C -UBT. Results of clinical follow-up of the CIU condition 3 and 6 months after the eradication were reported as complete

remission (CR; disappearance of urticaria, and medication not necessary), partial remission (PR; improvement of symptoms, but no-demand use of antihistamine agents required), or no improvement (NC; patients who were not classified as showing CR or PR).

DNA was extracted from each isolated *H. pylori* strain to test for the presence of the *cagA* gene. For each strain isolated from patients with CIU, we tested strains isolated from two sex- and age-matched control subjects. In brief, bacterial pellets were digested with 0.3 units of proteinase K at 55°C for 2 h and DNA was extracted with phenol-chloroform-isoamylalcohol. The presence of the *cagA* gene was determined by polymerase chain reaction (PCR) as described previously.¹¹

Statistical analysis

χ^2 Analysis was used to compare *H. pylori* seropositivity findings, and Fisher's exact probability test was used to compare *cagA*-positivity findings. The Mann-Whitney *U*-test was used to compare the results for improvement of CIU. A probability (*P*) value of less than 0.05 was considered significant.

Results

Of the 50 patients with CIU, 26 (52%) were *H. pylori*-seropositive, while 48 out of the 100 control subjects were *H. pylori*-seropositive (48%). The difference was not statistically significant (Table 1). *H. pylori* strains were isolated from gastric biopsy specimens of 13 patients and all the strains possessed the *cagA* gene. *H. pylori* strains obtained from 26 sex- and age-matched control subjects were also *cagA*-positive.

Table 2 shows the effects of *H. pylori* eradication therapy on CIU. Nineteen out of the 26 patients infected with *H. pylori* received first-line eradication therapy, while 7 patients did not wish to receive eradication therapy. Eradication of *H. pylori* was achieved in 14 patients by first-line therapy. CR and PR and CIU were seen in 5 and 4 patients, respectively. After the failure of first-line therapy, 3 out of the 5 patients received second-line therapy. *H. pylori* was successfully eradicated in all 3 patients, and 1 patient showed CR and 1 patient showed PR. Finally, of the 17 *H. pylori*-eradicated patients with CIU, 6 patients showed CR

Table 1. Prevalence of IgG antibody against *Helicobacter pylori*

	No. of subjects (M/F)	Mean age; years (range)	Seropositivity
Chronic urticaria	50 (16/34)	48.2 (25–75)	52.0%
Control subjects	100 (32/68)	48.3 (24–76)	48.0%

Table 2. Effects of *H. pylori* eradication therapy on urticaria symptoms

	No. of subjects	Urticaria			CR + PR (%)
		CR	PR	NC	
Received eradication					
LPZ + AMOX + CLA					
Success	14	5	4	5	64.3
Failure	5	0	1	4	20.0
LPZ + AMOX + MNZ					
Success	3	1	1	1	66.7
Without eradication	7	0	1	6	14.3
<i>H. pylori</i> eradicated	17	6	5	6	64.7
<i>H. pylori</i> persisted	9	0	2	7	22.2

LPZ, lansoprazole; AMOX, amoxicillin; CLA, clarithromycin; MNZ, metronidazole; CR, complete remission; PR, partial remission; NC, no change

(35.3%) and 5 patients showed PR (29.4%) 3 to 6 months after the successful eradication therapy. On the other hand, PR of CIU was observed in 1 of 7 patients who did not wish to receive therapy for eradication of *H. pylori* and in 1 patient who failed first-line therapy. The proportion of patients with CR or PR was significantly higher in *H. pylori*-eradicated patients (64.7%) than in patients in whom *H. pylori* persisted (22.2%; $P < 0.02$). No patients showed worsening of symptoms after either of the eradication therapies.

Discussion

Since the time that early German studies demonstrated the regression of CIU by the eradication of *H. pylori*, a number of studies have investigated the association between *H. pylori* infection and CIU. Although the prevalence of *H. pylori* infection in patients with CIU has been compared with that in healthy subjects, the results are controversial.^{2,8} In Japan, the prevalence of anti-*H. pylori* IgG antibody in patients with CIU has been studied in only one area, and was described as lower (56%) than that in the asymptomatic Japanese population (70%–80%).^{9,10} In the present study, we conducted a case-control comparison to examine *H. pylori* seropositivity in patients with CIU, because the prevalence of *H. pylori* infection is very high in the elderly in Japan. Control subjects were selected from patients who had undergone endoscopy, in order to include only patients without gastroduodenal lesions, which are associated with *H. pylori* infection. Finally, *H. pylori* seropositivity in patients with CIU was not different from that in control subjects in this series of patients. From our results and results from another Japanese population in previous studies, it appears that patients with CIU may not have a higher prevalence of *H. pylori* infection compared with the general population in Japan.

Early studies had shown a high success rate of clinical remissions of CIU after eradication therapy in patients with *H. pylori* infection.^{2–5} However, more recent studies sometimes failed to support the therapeutic effects of *H. pylori* eradication for CIU.^{6–8} Differences in eradication regimens may be associated with such controversial results, because it is possible that other underlying focal infections were cured by antibiotics. At present, in Japan, 1-week of triple therapy of AMOX and CLA with a PPI is the only regimen that is approved by the Japanese system of health insurance for the eradication of *H. pylori*.¹² Although triple therapy of PPI, AMOX, and CLA has been used for patients with CIU in previous studies, including two Japanese studies, the dose of antibiotics and/or the duration of the treatment were not the same as the Japanese standard regimen. In the present study, to examine the therapeutic effects of the Japanese standard regimen on CIU, initial eradication was performed by 1 week of LPZ (30 mg b.d.), AMOX (750 mg b.d.), and CLA (200 mg b.d.). Our results demonstrated higher complete and partial remission rates of CIU in patients in whom the Japanese standard eradication regimen succeeded compared with the rates in the patients in whom *H. pylori* was not eradicated. Thus, to eradicate *H. pylori* in patients with CIU, the regimen approved by the Japanese system of health insurance would be useful. Furthermore, improvement of CIU was also seen in two out of three patients who were treated with MNZ instead of CLA. Our results and previous Japanese studies support the association between *H. pylori* infection and CIU in certain patients with CIU in Japan.

At present, the pathogenic roles of *H. pylori* infection in CIU remain unclear. Although several studies have been performed to identify immunoglobulin-binding antigenic structures of *H. pylori*,^{13,14} little is known about the antigenic structures that are responsible for CIU. Another possible mechanism is the increase of gastric

permeability. Several studies have demonstrated that gastric permeability is increased in the *H. pylori*-infected stomach and is decreased by eradication of *H. pylori*.^{15,16} Recognition of food allergens may occur more easily in gastric mucosa infected with *H. pylori*. In addition, in *H. pylori*-infected gastric mucosa, proinflammatory cytokines are also increased, and this may contribute to enhance systemic inflammatory responses. If these mechanisms are important in the pathogenesis of CIU in patients with *H. pylori* infection, it is possible that more intense gastric inflammation would be seen in patients with CIU than in those without the disease. However, few studies have investigated the association between CIU and the degree of gastric mucosal inflammation, or the association between CIU and phenotypes of *H. pylori*, such as *cagA*. In the present study, we examined the presence of the *cagA* gene, and all the strains tested were *cagA*-positive, both in patients with CIU and in control subjects, as previously described.¹⁷ Thus, it was difficult to find any associations between bacterial possession of the *cagA* gene and CIU in Japan. It would be of interest to study the association between virulent phenotypes and CIU in populations which do not have a high prevalence of virulent strains.

In conclusion, the prevalence of *H. pylori* infection in patients with CIU was not higher than that in the general population. However, eradication of *H. pylori* would be a valid choice for the treatment of CIU if patients are infected with *H. pylori*, and the Japanese standard triple therapy would be useful. The mechanisms of how *H. pylori* infection induces CIU should be elucidated to understand why the eradication of *H. pylori* has therapeutic effects on CIU although the prevalence of *H. pylori* is not high in patients with CIU.

References

1. Malfertheiner P, Megraud F, O'Morain C, Hungin AP, Jones R, Axon A, et al. Current concepts in the management of *Helicobacter pylori* infection—the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 2002;16:167–80.
2. Wedi B, Wagner S, Werfel T, Manns MP, Kapp A. Prevalence of *Helicobacter pylori*-associated gastritis in chronic urticaria. *Int Arch Allergy Immunol* 1998;116:288–94.
3. Rebora A, Drago F, Parodi A. May *Helicobacter pylori* be important for dermatologists? *Dermatology* 1995;191:6–8.
4. Tebbe B, Geilen CC, Schulzke JD, Bojarski C, Radenhausen M, Orfanos CE. *Helicobacter pylori* infection and chronic urticaria. *J Am Acad Dermatol* 1996;34:485–6.
5. Di Campli C, Gasbarrini A, Nucera E, Franceschi F, Ojetti V, Sanz Torre E, et al. Beneficial effects of *Helicobacter pylori* eradication on idiopathic chronic urticaria. *Dig Dis Sci* 1998;43:1226–9.
6. Howden CW. No evidence for an association between *H. pylori* and idiopathic chronic urticaria. *Dig Dis Sci* 1999;44:485–6.
7. Wustlich S, Brehler R, Luger TA, Pohle T, Domschke W, Foerster E. *Helicobacter pylori* as a possible bacterial focus of chronic urticaria. *Dermatology* 1999;198:130–2.
8. Dauden E, Jimenez-Alonso I, Garcia-Diez A. *Helicobacter pylori* and idiopathic chronic urticaria. *Int J Dermatol* 2000;39:446–52.
9. Shiotani A, Okada K, Yanaoka K, Itoh H, Nishioka S, Sakurane M, et al. Beneficial effect of *Helicobacter pylori* eradication in dermatologic diseases. *Helicobacter* 2001;6:60–5.
10. Sakurane M, Shiotani A, Furukawa F. Therapeutic effects of antibacterial treatment for intractable skin diseases in *Helicobacter pylori*-positive Japanese patients. *J Dermatol* 2002;29:23–7.
11. Peek RM Jr, Miller GG, Tham KT, Perez-Perez GI, Cover TL, Atherton JC, et al. Detection of *Helicobacter pylori* gene expression in human gastric mucosa. *J Clin Microbiol* 1995;33:28–32.
12. Satoh K. Indications for *Helicobacter pylori* eradication therapy and first-line therapy regimen in Japan: recommendation by the Japanese Society for *Helicobacter pylori*. *J Gastroenterol* 2002;37(Suppl 13):34–8.
13. Liutu M, Kalimo K, Uksila J, Savolainen J. Extraction of IgE-binding components of *Helicobacter pylori* by immunoblotting analysis in chronic urticaria patients. *Int Arch Allergy Immunol* 2001;126:213–7.
14. Bakos N, Fekete B, Prohaszka Z, Fust G, Kalabay L. High prevalence of IgG and IgA antibodies to 19-kDa *Helicobacter pylori*-associated lipoprotein in chronic urticaria. *Allergy* 2003;58:663–7.
15. Gasbarrini A, Franceschi F, Gasbarrini G, Pola P. Extraintestinal pathology associated with *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol* 1997;9:231–3.
16. Goodgame RW, Malaty HM, el-Zimaity HM, Graham DY. Decrease in gastric permeability to sucrose following cure of *Helicobacter pylori* infection. *Helicobacter* 1997;2:44–7.
17. Shimoyama T, Fukuda S, Tanaka M, Mikami T, Saito Y, Munakata A. High prevalence of the *cagA*-positive *Helicobacter pylori* strains in Japanese asymptomatic patients and gastric cancer patients. *Scand J Gastroenterol* 1997;32:465–8.