

Effect of *Helicobacter pylori* Eradication on Platelet Recovery in Patients With Chronic Idiopathic Thrombocytopenic Purpura

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Background: A relationship between *Helicobacter pylori* infection and idiopathic thrombocytopenic purpura (ITP) has previously been reported. We determined the prevalence of *H pylori* infection in Japanese patients with chronic ITP and the effect of its eradication on platelet count.

Methods: The study population comprised 53 Japanese adults with chronic ITP and a platelet count of less than $100 \times 10^3/\mu\text{L}$. A ^{13}C -urea breath test was performed to determine *H pylori* infection status. Those patients who were *H pylori* positive gave written informed consent and received eradication therapy. The effect of *H pylori* eradication on platelet count was evaluated up to 6 months after therapy. Clinical parameters were compared between responders to the therapy (increase in platelet count) and nonresponders, as well as between *H pylori*-positive and -negative patients.

Results: Of the 53 patients with chronic ITP in the study, 39 (74%) were *H pylori* positive. Of the 32 infected patients who received treatment, *H pylori* was successfully eradicated in 27 patients (84%). In 10 (37%) of these patients, this resulted in a favorable platelet response. A partial response was seen in 5 additional patients (19%). A significant ($P < .001$) increase in platelet count was demonstrated in patients in whom *H pylori* was successfully eradicated but not in patients who were unsuccessfully treated or in untreated patients. Current corticosteroid therapy was reported more often in nonresponders than in responders.

Conclusion: Eradication of *H pylori* may prove effective in increasing platelet count in *H pylori*-positive patients with chronic ITP.

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HELICOBACTER PYLORI IS A recognized cause of gastroduodenal disorders including gastritis, peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue lymphoma (MALToma). Eradication of this bacterium may contribute to histological improvement of gastritis,¹ reduction in peptic ulcer recurrence,² and remission of MALToma.³ In recent years, several studies have investigated the relationship between *H pylori* and extragastroduodenal disorders, including autoimmune-associated diseases. With regard to idiopathic thrombocytopenic purpura (ITP), which is induced by autoantibodies against platelets, studies to determine the effect of *H pylori* eradication on platelet recovery have provided conflicting results.⁴⁻¹⁰ To clarify the relationship between *H pylori* infection and ITP, we determined the prevalence of *H pylori* infection in Japanese patients with chronic ITP and the effect of its eradication on platelet recovery. Moreover, we

compared the clinical parameters between responders to the therapy (increase in platelet count) with nonresponders.

METHODS

PATIENTS

The study population comprised 53 adult Japanese patients (16 men and 37 women) with chronic ITP. All of these patients had previously been diagnosed as having chronic ITP according to the American Society of Hematology guidelines,¹¹ and their platelet counts were less than $100 \times 10^3/\mu\text{L}$. Twenty-seven patients were receiving treatment with corticosteroids, and 10 had previously undergone splenectomy. No patients had a life-threatening hemorrhage or had required a change in treatment for the past 6 months. Patients were excluded from the study if they had previously received *H pylori* eradication therapy, reported drug allergies, or had serious disease, such as malignant tumors, or cardiac, renal, or hepatic disease. All patients gave informed consent to participate in this study.

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TESTS AT BASELINE

At baseline, a ^{13}C -urea breath test (^{13}C -UBT) was performed to detect *H pylori* infection, and platelet counts were measured in all patients. The ^{13}C -UBT was performed as follows: ^{13}C -urea was administered orally at a dose of 100 mg in 100 mL of distilled water, on an empty stomach and early in the morning. After thorough rinsing of the oral cavity, the patients rested in a left lateral position for 5 minutes, and then sat for 15 minutes. Expired air was then collected after a 10-second breath hold and analyzed with an infrared spectrometer (UBiT-IR300; Otsuka Denshi, Osaka, Japan). Measured values were expressed as $\Delta^{13}\text{C}\text{‰}$ (per million) 20 minutes after administration, with a cutoff of $\Delta 2.5\text{‰}$ (per million). Patients with $\geq \Delta 2.5\text{‰}$ were considered positive for *H pylori*, while those with $< \Delta 2.5\text{‰}$ were considered negative.

ERADICATION THERAPY FOR *H PYLORI*

Those patients who were found to be *H pylori* positive gave written informed consent and were treated for 7 days with lansoprazole, 30 mg twice daily, clarithromycin, 200 mg twice daily, and amoxicillin, 750 mg twice daily. This is a recommended regimen for *H pylori* eradication therapy according to the Japanese Society for *Helicobacter* Research.¹² After 1 and 6 months, another ^{13}C -UBT was performed to confirm the success of eradication therapy and ensure that recrudescence or reinfection had not occurred.

ASSESSMENT OF RESPONSE

Platelet counts were monitored every 2 weeks and assessed 6 months after the end of *H pylori* eradication therapy, and these counts were compared with those taken at baseline. A good response was defined as a platelet increase of greater than $100 \times 10^3/\mu\text{L}$ or an increase to within the normal range ($> 150 \times 10^3/\mu\text{L}$). A partial response was defined as an increase in the platelet count of 50 to $100 \times 10^3/\mu\text{L}$. No response was defined as no increase in the platelet count or an increase of less than $50 \times 10^3/\mu\text{L}$. Platelet counts were monitored in both *H pylori*-infected patients and uninfected individuals who were not treated with eradication therapy. The change in platelet count was compared between the following 4 groups: *H pylori* infected and successfully eradicated, *H pylori* infected and unsuccessfully treated, *H pylori* infected and untreated, and uninfected and untreated. Clinical parameters including age, sex, disease duration, platelet count at baseline, present corticosteroid therapy, and whether splenectomy had been previously performed were also compared between responders (good response + partial response) and nonresponders, as well as between *H pylori*-positive and -negative patients. Patients who were receiving continuous immunosuppressive therapy with corticosteroids continued their treatment throughout the study period.

STATISTICAL ANALYSIS

Differences in age, disease duration, and platelet count at baseline between groups were analyzed by the Mann-Whitney test, and differences in sex, present corticosteroid therapy, and previous splenectomy history were assessed using the χ^2 or Fisher exact probability test. Tests for a linear trend were applied to comparisons of the assessment of eradication therapy between the 4 groups. Changes in platelet count were examined by a repeated measures analysis of variance and by the Scheffé test. $P < .05$ was considered to be statistically significant in all tests.

Table 1. Characteristics in *Helicobacter pylori*-Positive and -Negative Patients With Chronic ITP

Characteristic	<i>H pylori</i> -Positive (n = 39)	<i>H pylori</i> -Negative (n = 14)	P Value
Age at entry, mean (range), y	62.0 (37-87)	52.4 (39-77)	.01
Sex (male/female)	14/25	2/12	.19
Disease duration, mean (range), mo	59.4 (6-264)	131.6 (15-310)	.001
Platelet count at entry, mean (range), $\times 10^3/\mu\text{L}$	55 (19-99)	56 (20-97)	.94
Previous splenectomy, No. (%)	6 (15)	4 (29)	.43
Present corticosteroid therapy, No. (%)	19 (49)	8 (57)	.76

Abbreviation: ITP, idiopathic thrombocytopenic purpura.

RESULTS

PREVALENCE OF *H PYLORI* INFECTION AND RESULTS OF TREATMENT

Of the 53 patients tested using the ^{13}C -UBT, *H pylori* was detected in 39 (74%). Of the 39 patients with confirmed *H pylori* infection, 32 gave written informed consent for eradication therapy. Successful eradication was achieved in 27 patients (84%). Neither severe adverse effects nor a decrease in the platelet count occurred in any patient receiving eradication therapy. There was no recrudescence of *H pylori* infection in any treated patient at 6 months after therapy.

The clinical parameters in *H pylori*-positive and -negative patients are given in **Table 1**. Age at the time of study was significantly greater and ITP duration shorter in *H pylori*-positive than in *H pylori*-negative patients. In other words, the age at onset was higher in *H pylori*-positive patients. There was no significant difference between groups with respect to sex, platelet count, or the report of previous splenectomy or present corticosteroid therapy.

RESPONSE TO ERADICATION THERAPY

In those patients in whom *H pylori* was successfully eradicated, a good response was seen in 10 (37%) and a partial response in 5 (19%). A platelet response was not evident in those infected patients in whom eradication therapy had been unsuccessful or in untreated patients (**Table 2**).

A significant ($P < .001$) increase in platelet count was found even 1 month after successful *H pylori* therapy, and this was maintained beyond 6 months after treatment. There was no significant change in platelet counts in those patients in whom *H pylori* was not successfully eradicated ($P = .63$) or in untreated ($P = .56$) patients (**Figure**). The increased platelet count was maintained for an average follow-up period of 12 months in all 15 patients who had responded to eradication therapy.

Of the 27 successfully treated patients, 15 (56%) were judged to be responders and 12 (44%) nonresponders. There was no significant difference between the groups

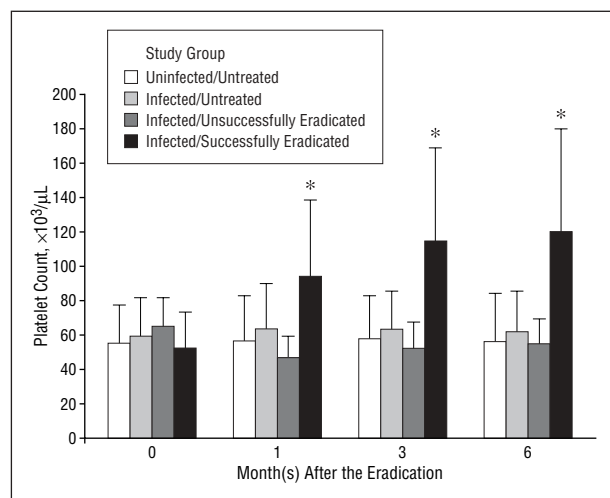
Table 2. Response to *Helicobacter pylori* Eradication Therapy in Patients With Chronic ITP*

Patient Group	Good Response	Partial Response	No Response	P Value for Trend
<i>H pylori</i> positive				
Successfully eradicated	10/27 (37)	5/27 (19)	12/27 (44)	
Unsuccessfully eradicated	0/5 (0)	0/5 (0)	5/5 (100)	.04†
Not treated	0/7 (0)	0/7 (0)	7/7 (100)	.02†
<i>H pylori</i> negative/ not treated	0/14 (0)	0/14 (0)	14/14 (100)	.001†

Abbreviation: ITP, idiopathic thrombocytopenic purpura.

*Data are number (percentage) of patients unless otherwise indicated.

†Versus successfully eradicated group.



Change in platelet counts over time. A significant increase in the platelet count was evident after 1 month of therapy in those patients who had been successfully treated. The increased platelet count was maintained beyond 6 months. The platelet counts did not change significantly in unsuccessfully treated patients or in untreated patients. The asterisk indicates $P < .001$ vs the initial count.

with regard to age, sex, disease duration, platelet count at entry, and previous splenectomy, while present corticosteroid therapy was slightly more common in non-responders than in with responders ($P = .05$).

COMMENT

In recent years, there have been several published studies reporting the prevalence of *H pylori* infection and the effect of its eradication in patients with chronic ITP. Results of 3 Italian studies showed a correlation between the presence of *H pylori* infection and chronic ITP. Gasbarrini et al⁴ reported that 61% of 18 patients with ITP (mean age, 45 years) were infected with *H pylori*, and in 8 patients in whom successful eradication was achieved there was a significant increase in platelet count 4 months after therapy. Emilia et al⁵ more recently demonstrated that 43% of 30 patients with ITP (mean age, 50 years) were infected with *H pylori*, and platelet recovery occurred in 50% of 12 treated patients. Veneri et al⁶ showed that the effect of *H pylori* eradication on platelet count

did not depend on the severity of ITP. An improvement in the platelet count after successful eradication was observed in 71% of 7 previously untreated patients, 75% of 4 relapsed patients after corticosteroid therapy, and 75% of 4 patients refractory to different treatment. In Japan, Kohda et al⁷ reported that *H pylori* infection was found in 63% of 40 ITP patients (mean age, 53 years), and 63% of the 19 treated patients showed a significant increase in platelet count. Results of 2 studies have also been published that support platelet recovery in ITP patients following *H pylori* eradication. Hino et al⁸ and Hashino et al⁹ demonstrated that *H pylori* was detected in 70% (21 of 30) (mean age, 54 years) and 64% (14 of 22) (mean age, 49 years) of the patients, respectively, and platelet recovery was obtained in 56% (10 of 18) and 38% (5 of 13) of successfully treated patients, respectively. In the present larger study, 39 (74%) of the 53 patients (mean age, 59 years) were *H pylori* positive, and platelet recovery occurred in 15 (56%) of the 27 successfully treated patients. The prevalence of *H pylori* has been reported to be 70% to 80% in healthy individuals born before 1950, but 25% to 45% in those born after this time.¹³ In the present study, the high prevalence of infection compared with that reported in comparable Japanese studies⁷⁻⁹ may reflect the older population studied here. Interestingly, platelet recovery following eradication therapy occurred at a similar rate in the present study to that previously reported in 5 studies from countries in which the prevalence of *H pylori* infection in the healthy population is generally high.^{13,14} Conversely, results of a Spanish study demonstrated that recovery of the platelet count was found in only 13% of 23 successfully treated patients, although prevalence of the infection was high (71%).¹⁰

In the present study, we assessed the change in platelet count over time in 4 groups: *H pylori* infected and successfully eradicated, *H pylori* infected and unsuccessfully treated, *H pylori* infected and untreated, and uninfected and untreated patients. Since a significant ($P < .001$) increase in platelet count was demonstrated in those patients in whom *H pylori* was successfully eradicated but not in those in whom eradication was unsuccessful or in untreated patients, it is strongly suggested that the recovery in the platelet count is the result of eradication of *H pylori*.

Although ITP in adults is typically a chronic disease, spontaneous remission or fatal hemorrhage has been shown to occur in a small percentage (5% and 5%, respectively).¹¹ Splenectomy and corticosteroid treatment have been considered therapies of choice for ITP, although corticosteroids have many potentially adverse effects such as hypercortisolism, osteoporosis, and immunosuppression. In addition, about 20% to 30% of patients are refractory to both therapies.¹⁵ In the present study, *H pylori* eradication therapy induced platelet recovery in more than half of the patients with chronic ITP, and severe adverse effects and a reduction in platelet count were not found during or after treatment in any patient who received therapy.

The mechanism by which *H pylori* may play a role in ITP pathogenesis remains unclear. A chronic immunological stimulus induced by *H pylori* or an immune mimicry between platelets and *H pylori* antigens has been

suggested as the cause of *H pylori*-induced ITP.¹⁶ Although it has been demonstrated that antibodies against *H pylori* cross-react with human tissues, such as gastric epithelial cells, ductal cells of salivary gland, and renal tubular cells,¹⁷ there is no support of cross-reactivity with platelets. In the present study, a significant ($P < .001$) increase in platelet count was evident as soon as 1 month after successful eradication of *H pylori*. This finding suggests that a cross-reaction between anti-*H pylori* antibodies and platelets is not the only feasible mechanism of *H pylori*-induced thrombocytopenia, since a significant reduction of the titer of *H pylori* antibodies has been demonstrated more than 6 months after eradication therapy.¹⁸ From a genetic standpoint, differences in HLA class II allele patterns have been shown to be associated with *H pylori* infection status.¹⁹ Furthermore, cytokines and chemokines produced in the gastric mucosa in response to *H pylori* infection^{20,21} may play a role in the immune response involved in ITP pathogenesis. Levels of serum cytokines, such as interferon- γ , interleukin (IL) 2, IL-4, and IL-6, have not, however, been shown to be different between *H pylori*-positive and -negative groups or between responders and nonresponders.⁹ Clinically, age at ITP onset tended to be higher in *H pylori*-positive patients than in -negative patients in the present and previous studies.^{7,22} This may be the result of long-term infection with *H pylori* providing suitable conditions for *H pylori*-induced thrombocytopenia.

We examined the differences in clinical parameters between responders and nonresponders to determine whether it may be possible to identify those patients likely to respond to therapy. However, we found no significant difference between groups, except in the proportion taking corticosteroid therapy.

In conclusion, eradication of *H pylori* in those infected patients with ITP may be effective in increasing the platelet count, even though the pathogenesis of *H pylori*-induced ITP remains unknown. Further studies are needed to clarify the long-term effect of eradication therapy and to identify factors that may assist in selecting patients with ITP who are more likely to respond to the treatment.

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