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

Ryugo Sato, MD; Kazunari Murakami, MD; Koichiro Watanabe, MD; Tadayoshi Okimoto, MD; Hajime Miyajima, MD; Masao Ogata, MD; Eiichi Ohtsuka, MD; Masaaki Kodama, MD; Yoshi Saburi, MD; Toshio Fujioka, MD; Masaru Nasu, MD

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 × 10^3/µL. A 13C-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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H 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, reduction in peptic ulcer recurrence, and remission of MALToma. In recent years, several studies have investigated the relationship between H pylori and extragastrointestinal 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. 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 and their platelet counts were less than 100 × 10^3/µL. 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.
At baseline, a 13C-urea breath test (13C-UBT) was performed to detect H pylori infection, and platelet counts were measured in all patients. The 13C-UBT was performed as follows: 13C-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 Den-shi, Osaka, Japan). Measured values were expressed as Δ13C‰ (per million) 20 minutes after administration, with a cutoff of Δ2.5‰ (per million). Patients with Δ ≥ 2.5‰ were considered positive for H pylori, while those with Δ < 2.5‰ 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. After 1 and 6 months, another 13C-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 x 10³/µL or an increase to within the normal range (>150 x 10³/µL). A partial response was defined as an increase in the platelet count of 50 to 100 x 10³/µL. No response was defined as no increase in the platelet count or an increase of less than 50 x 10³/µL. 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 χ² 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 Scheffe test. P < .05 was considered to be statistically significant in all tests.

PREVALENCE OF H PYLORI INFECTION AND RESULTS OF TREATMENT

Of the 53 patients tested using the 13C-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 1. Characteristics in Helicobacter pylori–Positive and –Negative Patients With Chronic ITP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>H pylori–Positive (n = 39)</th>
<th>H pylori–Negative (n = 14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry, mean (range), y</td>
<td>62.0 (37-87)</td>
<td>52.4 (39-77)</td>
<td>.01</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>14/25</td>
<td>2/12</td>
<td>.19</td>
</tr>
<tr>
<td>Disease duration, mean (range), mo</td>
<td>59.4 (6-264)</td>
<td>131.6 (15-310)</td>
<td>.001</td>
</tr>
<tr>
<td>Platelet count at entry, mean (range), x10³/µL</td>
<td>55 (19-99)</td>
<td>56 (20-97)</td>
<td>.94</td>
</tr>
<tr>
<td>Previous splenectomy, No. (%)</td>
<td>6 (15)</td>
<td>4 (29)</td>
<td>.43</td>
</tr>
<tr>
<td>Present corticosteroid therapy, No. (%)</td>
<td>19 (49)</td>
<td>8 (57)</td>
<td>.76</td>
</tr>
</tbody>
</table>

Abbreviation: ITP, idiopathic thrombocytopenic purpura.

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H pylori infection. 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 postulated for years. A recent study demonstrated that the presence of H pylori infection can trigger an immune response, leading to the release of cytokines that may stimulate the production of autoantibodies against platelet receptors. This immune response may contribute to the development of ITP, as demonstrated in a study by Veneri et al. These researchers found that patients with ITP had a higher prevalence of H pylori infection compared to a control group, and that successful eradication of H pylori was associated with an increase in the platelet count. The mechanism by which H pylori infection leads to an immune response against platelets is not fully understood, but it is thought to involve the presence of shared epitopes between H pylori and platelet membrane proteins. These shared epitopes can lead to the stimulation of autoreactive lymphocytes, which can recognize and activate platelets through the release of cytokines and other inflammatory mediators. The inflammatory response can then lead to the formation of platelet aggregates, which can decrease the number of circulating platelets and contribute to the development of thrombocytopenia. In addition, the inflammatory response can also lead to the activation of the coagulation cascade, which can further contribute to the formation of platelet aggregates and the development of thrombocytopenia. The role of H pylori infection in the pathogenesis of ITP needs to be further investigated to better understand the mechanisms involved and to develop more effective therapeutic strategies for patients with this condition.
suggested as the cause of *H pylori*–induced ITP. 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, 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. From a genetic standpoint, differences in HLA class II allele patterns have been shown to be associated with *H pylori* infection status. Furthermore, cytokines and chemokines produced in the gastric mucosa in response to *H pylori* infection 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. Clinically, age at ITP onset tended to be higher in *H pylori*–positive patients than in –negative patients in the present and previous studies. 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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Correspondence: Ryugo Sato, MD, Second Department of Internal Medicine, Faculty of Medicine, Oita University, Hasama-machi, Oita 879-5593, Japan (ryu5@med.oita-u.ac.jp).

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