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ORIGINAL ARTICLE

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Randomized study of *Helicobacter pylori* eradication therapy and proton pump inhibitor monotherapy for idiopathic thrombocytopenic purpura

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Abstract *Helicobacter pylori* (HP) eradication therapy is a useful treatment for idiopathic thrombocytopenic purpura (ITP). Some investigators have also reported the effects of proton pump inhibitor (PPI) monotherapy on ITP. We performed a randomized study of HP eradication therapy and PPI monotherapy on ITP. Four of nine patients achieved complete remission (CR), two of nine achieved partial remission (PR) in HP eradication therapy, three of eight achieved CR, and two of eight achieved PR in PPI monotherapy. No significant differences were observed in the CR + PR of these patients between HP eradication therapy and PPI monotherapy. As for cost comparisons, HP eradication therapy is cheaper than PPI monotherapy, but it is less effective.

Keywords Proton pump inhibitor (PPI) · Idiopathic thrombocytopenic purpura (ITP) · *Helicobacter pylori* (HP) · PA-IgG · HP eradication therapy

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Introduction

Idiopathic thrombocytopenic purpura (ITP) is an acquired bleeding disorder in which platelet destruction is induced by antiplatelet antibodies whose development mechanism is still poorly understood. Recently, some investigators have reported the efficacy of *Helicobacter pylori* (HP) eradication for ITP [1–12]. These reports suggest that some ITP populations developed autoantibodies to platelets after HP infection. However, these results are still controversial, and relapse and refractory ITP were also seen [4, 13, 14]. Recently, we and other investigators reported the effectiveness of proton pump inhibitors (PPI; omeprazole and lansoprazole) for ITP with HP infection [15–17]. Based on these reports, we compared the treatment efficacy and benefit of HP eradication therapy with PPI monotherapy.

Patients and methods

Patients

From November 2002 to June 2003, we investigated gastric HP infections in 25 adult thrombocytopenia patients. ITP was diagnosed on the basis of the presence of isolated thrombocytopenia (platelets<100×10^9/L) and megakaryocytic bone marrow hyperplasia or normoplasia. Other causes of thrombocytopenia (drugs, pseudothrombocytopenia, hepatitis C virus infections, human immunodeficiency virus infections, autoimmune disorders, malignancy, etc.) were excluded. Seventeen recently diagnosed patients (12 women and 5 men) were enrolled in this study according to the exclusion criteria. Their data are shown in Table 1. All these patients were initially treated with either HP eradication therapy or PPI monotherapy. They ranged from 49 to 89 years old, and their mean age was 61.7. Their platelet counts ranged from 2.9 to 7.4×10^9/L, and platelet-associated immunoglobulin G (PA-IgG) ranged from 18.6 to 292.0 ng/10^7 cells. All

Table 1 Patient's characteristics

No.	Age	Gender	Treatment (eradication: +/lansoprazole: L)	Platelet count before this study (10^9/L)	PA IgG before this study (ng/10^7 cells)	Anti-HP antibody before this (EV)	Hp eradication (success: S/failure: F)
1	51	Male	+	4.0	52.3	4.4	S
2	72	Female	+	4.7	180.8	4.5	S
3	62	Female	+	5.7	61.9	3.0	S
4	67	Female	+	5.0	58.6	6.2	F
5	50	Male	+	7.1	32.2	2.5	S
6	51	Female	+	6.0	58.6	4.7	F
7	77	Female	+	5.7	46.5	4.3	F
8	55	Female	+	6.0	29.3	5.4	F
9	58	Female	+	4.2	80.5	4.6	F
10	89	Female	L	4.9	47.7	4.4	S
11	55	Female	L	6.2	28.5	5.3	F
12	70	Female	L	4.1	265.3	6.2	F
13	56	Male	L	5.6	33.8	5.1	F
14	49	Female	L	7.4	82.9	6.7	F
15	58	Female	L	4.5	292.0	4.9	F
16	60	Male	L	7.4	18.6	5.9	F
17	69	Male	L	2.9	94.9	5.7	F

these patients were positive for anti-HP antibodies, and the titer of the anti-HP antibodies ranged from 2.5 to 6.7 EV.

Treatment

After this study had been approved by the institutional review board, informed consent was obtained from the patients, who were then enrolled and randomized into groups of HP eradication therapy or PPI monotherapy. Nine of 17 patients were administered HP eradication therapy (lansoprazole at 30 mg o.d., amoxicillin at 750 mg b.i.d., and clarithromycin at 200 mg b.i.d.) for seven consecutive days based on previous reports [18, 19]. The other patients were only administered lansoprazole (30 mg/day) daily, continuously if possible.

Response criteria

We did not use the urea breath test to monitor HP infection because of the continuous administration of PPI in the PPI monotherapy group. HP eradication achievement was assessed by monthly observation of anti-HP antibody titer. Platelet counts were also assessed monthly. The evaluation of platelet recovery effects was assessed as follows [20]: a complete remission (CR) was defined as the achievement of a platelet count more than 120×10^9/L, a partial remission (PR) was defined as a platelet count of less than 120×10^9/L, and an absolute increase was defined as a platelet count with a net increase greater than 30×10^9/L or a 50% increase in the platelet count with a net increase of 10×10^9/L but less than 30×10^9/L. Improvement had to have lasted for at least 1 month following HP eradication without any changes in therapy for ITP.

Statistical analysis

Statistical test was performed with StatView software (Brain Power, Calabasas, CA, USA), and data were expressed as mean±SD or median (range). Statistically significant differences in continuous data between HP eradication therapy and PPI monotherapy were determined by Student's *t* test. A *P* value of less than 0.05 was considered statistically significant in all tests.

Results

Comparisons of the two groups at treatment onset

Table 2 shows a comparison of these two groups. No significant differences were seen by age, gender, platelet count, or observation time. Mean PA-IgG level was higher

Table 2 Comparison of patient's characteristics

	HP eradication therapy	Lansoprazole alone	P
Mean Age (range)	60.3 (50-77)	63.3 (49-89)	0.60
Gender (male/female)	2/7	3/5	0.52
Platelet count at onset	5.38	5.38	1.00
Anti-HP antibody at onset	4.40	5.53	0.029
PA-IgG at onset	66.7	108.1	0.31
Observation time after treatment of this study (months)	16.9 (12-25)	12.5 (3-22)	0.22

Table 3 Comparison of treatment outcomes of patients

	HP eradication theraphy	Lansoplazole alone	P
HP eradication	4/9	1/8	0.17
CR	4/9	3/8	0.79
CR+PR	6/9	5/8	0.87
PA-IgG after treatment ($ng/10^7$ cells)	71.3	58.9	0.64
CR+PR one month after treatment	6/9	1/8	0.17
CR+PR three months after treatment	3/9	3/8	0.87
CR+PR six months after treatment	4/9	3/7	0.64
Recurrence	2/6	2/5	0.84

in the lansoprazole group, but no significant difference was observed. Only the titer of the anti-HP antibody was lower in the HP eradication therapy group (P=0.029) than that in the PPI monotherapy group.

Treatment outcomes of these two groups

Table 3 shows a comparison of the treatment outcomes of these two groups. In four of nine patients, HP was eradicated by HP eradication therapy, and in one of eight patients, HP was eradicated by PPI monotherapy. The success rate of HP eradication tended to be superior in the HP eradication therapy group, but no significant difference was observed. No significant differences were seen in the CR rates, the PA-IgG titer after treatment, the CR + PR rates 3 and 6 months after treatment, and the recurrence. The rates of CR + PR 1 month after treatment tended to be superior in HP eradication therapy, but no significant difference was observed. No adverse effects were observed in these patients.

Comparisons of responders and nonresponders

Table 4 compares the characteristics of patients with CR or PR and patients with no response. No significant differences were seen by age, gender, platelet count, anti-HP antibody titer at onset, or HP eradication. PA-IgG levels at onset and after treatment showed inferior tendencies in CR + PR patients, but no significant difference was observed. Platelet count 1 month after treatment showed superior tendencies in CR + PR patients, but no significant difference was observed. Platelet counts 3 and 6 months after treatment were superior in CR + PR patients (3 months, P=0.067; 6 months, P=0.029).

Discussion

Idiopathic thrombocytopenic purpura is an autoimmune disease caused by immunoglobulins that bind to platelets, which are destroyed by the reticuloendothelial system [21–23]. However, the disease's mechanism remains unclear. In recent years, several investigators have detected a relationship between HP infection and ITP because approximately 80% of HP-positive patients with ITP showed increased platelet counts after the eradication of HP infection with a 1- to 2-week cocktail of PPIs; antibiotics were used without immunosuppressive therapy with a wide range of response rates (13–100%) [1–12, 24].

Michel et al. [25] reported that the effects of steroid therapy were not different between HP-positive and HP-negative patients. On the other hand, ITP patients' refractory to steroid treatment dramatically improved platelet counts, freeing them from immunosuppressive therapy by HP eradication therapy [6, 26].

Recently, we and other investigators reported the effectiveness of PPIs (omeprazole and lansoprazole) for ITP with HP infection [15–17]. We found that the serum levels of anti-HP antibodies and PA-IgG gradually reduced after the administration of lansoprazole. Platelet count was elevated basing on the reduction of the anti-HP antibodies. This result suggests that lansoprazole is effective against HP infections and that the reduction of PA-IgG levels may

Table 4 Comparison between responders and non-responders

	CR+PR	No response	P
Age	63.1 (51-89)	59.2 (49-77)	0.50
Gender (male/female)	4/7	1/6	0.43
Platelet count at onset (10^9/L)	5.15 (2.9-7.4)	5.8 (4.1-7.4)	0.32
PA-IgG at onset ($ng/10^7$ cells)	62.5 (29.3-180.8)	129.6 (32.2-292.0)	0.11
Anti-HP antibody at onset (EV)	4.96 (3.0-6.2)	4.88 (2.5-6.7)	0.90
HP eradication	4/11	1/7	0.43
PA-IgG after treatment ($ng/10^7$ cells)	54.6 (18.5-153.4)	90.1 (52.7-181.0)	0.19
Platelet count one month after treatment (10^9/L)	9.71 (5.5-18.8)	6.83 (3.7-8.9)	0.16
Platelet count three months after treatment (10^9/L)	11.7 (5.2-21.6)	6.78 (3.9-10.1)	0.067
Platelet count six months after treatment (10^9/L)	13.5 (8.4-22.0)	6.90 (4.4-8.9)	0.029

reflect a reduction of HP infections. However, anti-HP antibody titer was not deleted in this case [17]. In the analysis of this study, platelet recovery was observed in two patients with respect to the reduction of anti-HP antibodies; one patient had platelet recovery after the reduction of the titer of the anti-HP antibodies, but the changes in the titer of anti-HP antibodies in the other five patients did not exactly parallel platelet recovery (data not shown). This result suggests that lansoprazole may have some other effect, such as immunosuppression, on ITP patients. We assume that long-term PPI administration therapy induces some other effects compared with HP eradication therapy.

In this study, five of eight patients who were administered lansoprazole monotherapy achieved CR + PR, and six of nine who were administered HP eradication therapy achieved CR + PR. No significant differences were seen in the treatment efficacy of these two groups. When comparing the cost benefits of these therapies, HP eradication therapy's total cost was \$38.70, which is much cheaper than lansoprazole monotherapy's monthly cost of \$139.90. No significant differences were seen in CR + PR 1 month after the treatment between two groups. However, CR + PR tendencies were superior in HP eradication therapy, suggesting that treatment response was faster in HP eradication therapy. When CR + PR patients were compared with other patients, no significant difference in HP eradication was shown. In this study, when HP eradication was only determined by anti-HP antibodies in more-than-6-month follow-ups, four of the five relapsed ITP patients were positive for anti-HP antibodies in their clinical course. These facts suggest that HP eradication is not always necessary for platelet recovery, but it is necessary to obviate relapse. If HP eradication therapy is effective but relapses often develop, lansoprazole monotherapy is necessary for maintenance therapy for HP-positive ITP patients.

Although the same effect was observed in these therapies, treatment duration and best treatment dosage of lansoprazole monotherapy are still unknown. Therefore, HP eradication therapy containing antibiotics was still superior to lansoprazole monotherapy, even if the administration of antibiotics was unnecessary. This study was too small to clarify this question. A more sophisticated, larger study is necessary for such clarification.

This study compared CR + PR patients and other patients. No significant differences were seen in PA-IgG levels, but an inferior tendency was observed in the CR + PR patients. Significant differences were seen in platelet counts 3 and 6 months after treatment, and only two patients achieved CR + PR 6 months after treatment. These facts suggest that if neither treatment efficacy has been seen within at least 6 months, the therapy should be changed.

Based on our experience, HP eradication therapy and lansoprazole monotherapy exhibit almost the same treatment efficacy for HP-positive ITP patients. HP eradication therapy was more suitable for the treatment of HP-positive ITP patients in cost performance but not in treatment efficacy. Several administrations of HP eradication therapy in HP-positive ITP patients resulted in frequent recurrence or failure. In such cases, lansoprazole monotherapy for maintenance treatment may be the useful treatment option for HP-positive ITP patients. Since the number of patients was limited in this study, a larger study is needed.

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