Annals of Hematology (2022) 101:1435–1445
https://doi.org/10.1007/s00277-022-04782-2

ORIGINAL ARTICLE

Sequential eradication of *Helicobacter pylori* as a treatment for immune thrombocytopenia in patients with moderate thrombocytopenia: a multicenter prospective randomized phase 3 study

Boram Han[1] · Hyo Jung Kim[1] · Ho-Young Yhim[2] · Doyeun Oh[3] · Sung Hwa Bae[4] · Ho-Jin Shin[5] · Won-Sik Lee[6] · JiHyun Kwon[7] · Jeong-Ok Lee[8] · Hwa Jung Kim[9,10] · Soo-Mee Bang[8]

Received: 16 May 2021 / Accepted: 1 February 2022 / Published online: 28 May 2022

Abstract

Due to several issues, standard treatments are not recommended for asymptomatic patients with moderate immune thrombocytopenia (ITP). Since platelet responses are reported in some patients with *Helicobacter pylori* (*H. pylori*)-positive ITP after eradication, we conducted a multicenter, phase 3 study to evaluate the safety and efficacy of recently established sequential eradication for these patients having moderate thrombocytopenia. Persistent or chronic ITP patients with platelet count ($30\times10^3\sim80\times10^3$/μL) and confirmed active *H. pylori* infection were randomly assigned to a treatment and a control group. The former received 10-day sequential treatment. Eradication was assessed by urea breath test at 3 months after treatment. Primary endpoint was the overall platelet response rate at 3 months in successfully eradicated treatment group and control group. Secondary endpoints were platelet response time, *H. pylori* eradication success rate, etc. The patient enrollment terminated early because of the change of national insurance and treatment guideline for *H. pylori*-positive patients in Korea during the study. Of the 28 *H. pylori*-positive ITP patients, 17 were randomized to the treatment group, and eradication was achieved for 15 (88.2%) at 3 months, and seven in control group after withdrawal. Statistically, significant difference in platelet response rates between the two groups were observed ($p=0.017$). Our study verifies that *H. pylori* eradication was an effective ITP treatment for patients with *H. pylori*-associated moderate ITP. This sequential eradication regimen showed not only a high *H. pylori* eradication rate, but also a remarkable platelet response for ITP patients. Trial registration number and date of registration for these prospectively registered trials is ClinicalTrials.gov number, NCT03177629 and June 6, 2017.

Keywords Immune thrombocytopenia · *Helicobacter pylori* · Eradication · Thrombocytopenia

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease [1, 2] with low platelet count, destroyed by anti-platelet antibodies, via autoreactivity expression of T and B cells, suppressing platelet production of megakaryocytes in the bone marrow and reducing platelets in peripheral blood. For primary ITP treatment, immunosuppressants such as steroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin are used. Adult ITP treatment guidelines recommend starting treatment when bleeding symptoms are noticed or when platelet count drops to 30×10^3/μL or less, taking into account the effectiveness of the treatment, toxicity, risk of bleeding without treatment, and cost-effectiveness [3, 4].

The association between ITP and *Helicobacter pylori* (*H. pylori*) has been reported. In 1998, Gasbarrini et al. [5] reported that *H. pylori* eradication as a treatment could improve thrombocytopenia in ITP patients. In 2009, a meta-analysis study reported that the platelet response rate was more than 50% by *H. pylori* eradication as a treatment [6–8]. Besides, platelet count improvement after *H. pylori* eradication as a treatment was 8.8% for *H. pylori*-negative ITP patients and 51.2% for *H. pylori*-positive ITP patients. The

Boram Han and Hyo Jung Kim contributed equally to this work.

✉ Soo-Mee Bang
smbang7@snu.ac.kr

Extended author information available on the last page of the article

odds ratio for this improvement was 14.5 (95% confidence interval: CI 4.2 ~ 83.0) [9]. However, most studies reporting the efficacy of *H. pylori* eradication as a treatment for ITP were retrospective, observational studies. There were only a few randomized studies or phase 2 and 3 studies [10–16].

Domestic and international guidelines for *H. pylori* eradication suggest standard 3-drug treatment including proton pump inhibitor (PPI) as the first-line treatment. The eradication failure rate is known to be about 20% [17]. The eradication success rate of the standard 3-drug treatment is decreasing due to an increase in antibiotic resistance [18, 19]. As an alternative to the primary treatment, sequential and concomitant treatment has been proposed [20, 21]. In the sequential treatment, PPI and amoxicillin are administered in the first half followed by administration of PPI, clarithromycin, and metronidazole in the second half. This method is superior to the standard 3-drug treatment and its effect persists even in a long-term observation [22–24]. A meta-analysis has reported that the sequential treatment has a higher elimination rate (79.4% vs. 68.2%) with similar compliance and side effects than the standard 3-drug treatment [25].

According to ITP treatment guidelines, treatment is not recommended for patients with moderate ITP with platelets greater than 30×10^3/ μL. Although such patients do not have severe bleeding symptoms, their physical and mental quality of life could be affected by procedures or surgery, vigorous physical activity, and restrictions on career options. Therefore, if long-term effective and safe treatment is developed, active treatment could be considered for this patient group instead of simple observation. Considering the cost, effectiveness, and side effects of *H. pylori* eradication therapy based on available data, it can be said that this therapy is close to an ideal treatment for *H. pylori*-positive ITP patients. However, existing studies have limited data on only moderate thrombocytopenia patients with ITP. Besides, there is currently no published study on whether platelet response is improved in *H. pylori*-positive ITP patients when sequential treatment as a new *H. pylori* eradication therapy is used. Therefore, we conducted a phase 3 study to confirm the efficacy and safety of *H. pylori*-positive ITP treatment in *H. pylori*-positive ITP patients with moderate thrombocytopenia using only sequential eradication treatment.

Methods

This was a prospective, multicenter, non-blind, randomized phase 3 study conducted in eight Korean institutions. The study protocol was approved by institutional review boards and registered with ClinicalTrials.gov (NCT03177629). All patients voluntarily decided to participate in this study, and written consents was obtained.

Eligible patients were adults over 19 years of age with persistent (lasting 3 to 12 months after diagnosis) or chronic (lasting more than 12 months after diagnosis) ITP as defined by the International Working Group and having platelet counts of 30×10^3/μL ~ 80×10^3/μL. Eligible patients were enrolled in this study when *H. pylori* was confirmed to be positive by urea breath test (UBT), rapid urease test, stool antigen test, or biopsy through gastroscopy. Exclusion criteria were previous *H. pylori* eradication treatment, any treatment for ITP within the last 3 months, an underlying disease or drug history that might cause secondary thrombocytopenia, a history of bleeding disease or at risk of bleeding from taking antithrombotic or aspirin.

The failure rate of *H. pylori* eradication therapy was assumed 20% for the treatment group. The randomization ratio between the treatment group and the control group was set to be 5:4. Patients were assigned to the treatment group or the control group according to a stratified block randomization table. Stratification factors were (1) the presence or absence of previous ITP treatment history and (2) platelets greater than 30×10^3/μL but less than 50×10^3/μL versus platelets greater than 50×10^3/μL but less than 80×10^3/μL.

The treatment group was sequentially administered four drugs as follows: pantoprazole 40 mg per os (PO) b.i.d., amoxicillin 1,000 mg PO b.i.d. for days 1–5, followed by pantoprazole 40 mg PO b.i.d., clarithromycin 500 mg PO b.i.d., and metronidazole 500 mg PO t.i.d. until days 6–10. At 3 months, success in both eradication and platelet response was confirmed in the treatment group. The control group was followed for the first 3 months. At 3 months, the same eradication treatment was performed for the control group as for the treatment group. At 6 months, eradication success and platelet response were checked.

The success of *H. pylori* eradication was confirmed as a negative result of UBT at 3 months of treatment. Platelet counts were checked at 1, 2, 3, and 6 months. Response evaluation followed the definition of the ITP treatment response evaluation criteria of the International Working Group. If the value of platelet count was more than 100×10^3/μL, it was called a complete response (CR). If it was more than 30×10^3/μL and at least two times higher than the baseline value, it was called response (R). If it did not meet the criteria of R, it was called no response (NR) [3]. Safety evaluation was performed for all patients who took the antibacterial treatment drug for more than one day. The severity of adverse events was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) (Version 4.0). Drug compliance was defined as taking 85% or more of the drug.

The primary objective was the overall response rate (CR + R) based on platelets at 3 months with successful eradication and confirmed UBT negative in the treatment group and control group. Secondary objectives were the

time to platelet response, success rate of *H. pylori* eradication, clinical characteristics between platelet responders, and non-responders after treatment, safety, and drug compliance. Among the clinical features of enrolled patients, the hemorrhagic symptom score was measured before and after treatment using the clinical hemorrhage scoring system [26].

The platelet response rate at 3 months was assumed 50% for the treatment group with successful eradication and 15% for the control group. The sample size of each group required to test this hypothesis at a one-sided significance level of 5% and power of 80% was 21 (actually, 27 in consideration of eradication failure rate in the treatment group). A total of 54 patients (30 in the treatment group and 24 in the control group) were enrolled in consideration of a 10% dropout rate.

Results of all patients included in the randomization were analyzed according to the intention-to-treat principle. Platelet responses in the treatment group of patients with *H. pylori* successfully eradicated, and the control group was analyzed by chi-square test or Fisher's exact test. Clinical difference between platelet responders and non-responders was analyzed by the Kruskal–Wallis test. The period until platelet response and the cumulative platelet response were analyzed by Gray's test. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA) (http://www.sas.com).

Results

A total of 28 participants (10 males and 18 females) were registered from May 2017 to May 2020. At the time of randomization (17 to the treatment group and 11 to the control group), the Korean national insurance and treatment guidelines for *H. pylori*-positive ITP patients were changed. Thus, subject registration was terminated early. Out of 17 subjects for the treatment group who received the eradication treatment, 15 were found to be UBT negative at 3 months, showing an *H. pylori* eradication rate of 88.2%. One patient had eradication failure and one patient dropped out due to worsening thrombocytopenia (Fig. 1). Four out of 11 control subjects withdrew their consent after randomization. Baseline disease characteristics such as age, previous ITP treatment history, baseline platelet counts, and hemorrhagic symptom score did not show statistically significant differences between the treatment group and the control group and between the treatment group with successful eradication and the control group (Table 1). Three patients in the treatment group and two patients in the control group received treatment before the study enrollment. Two received corticosteroid and IVIG; the other three received IVIG, eltrombopag, and danazol monotherapy, respectively.

At 3 months after the beginning of treatment, 9 out of 15 patients in the treatment group had successful eradication (UBT negative) with a CR (more than 100×10^3/μL platelets). The remaining six patients did not show a response based on platelet counts. All seven control subjects showed no response at 3 months based on platelet counts. Therefore, the platelet response rate at 3 months as the primary endpoint was 60% for the treatment group with successful eradication and 0% for the control group, showing a statistically significant difference ($p = 0.017$) (Fig. 1). The median difference (interquartile range, IQR) of the hemorrhagic symptom score between before and after treatment was 0.00 (0.00, 0.00) for the treatment group with successful eradication and 0.00 (–0.75, 0.00) ($p = 0.031$) for the control group. *H. pylori* eradication therapy, which had been planned with 3 months of follow-up, was performed for six out of seven control patients. Of these, three had UBT negative results at 6 months of follow-up. Platelet response was confirmed as CR in one patient.

Of all 23 patients who received the sequential treatment in both of the treatment group and the control group, 18 achieved successful eradication at 3 months after eradication, showing an *H. pylori* eradication rate of 78.3%. The platelet response rate 3 months after *H. pylori* eradication was 55.6% in both groups with successful eradication.

The median time to platelet response in patients with successful eradication was 2 months (95% CI: 0.49–3.52 months) (Fig. 2). Platelet response rates at 1 month, 2 months, 3 months, and 6 months were 33.3%, 53.3%, 60.0%, and 64.3%, respectively. Continuous platelet reactions were observed.

The median platelet counts (IQR) at 3 months of follow-up were 108.0×10^3/μL (46.5, 160.3) and 56.5×10^3/μL (50.3, 74.8) in the treatment group with successful eradication and the control group, respectively ($p = 0.070$), and those at 6 months were 139.5×10^3/μL (59.3, 152.5) and 66.0×10^3/μL (50.5, 106.8) ($p = 0.193$), with the treatment group showing a tendency to have higher platelet counts than that of control group.

The drug compliance was 95.7% for 17 patients in the treatment group and six patients in the control group who underwent eradication at 3 months. Of all patients, 78.3% completed the full dose according to the planned regimen. During treatment, adverse events caused by drugs were mainly gastrointestinal symptoms, with nausea being the most frequent. All adverse events were tolerable with grades 1 and 2 (Table 2).

To determine which factors influenced platelet response, post hoc analysis of clinical and laboratory factors was performed for patients with platelet response at 3 months of follow-up [platelet responder group, 9] and those in the platelet non-responder group [14] regardless of the presence or absence of *H. pylori* eradication treatment or the

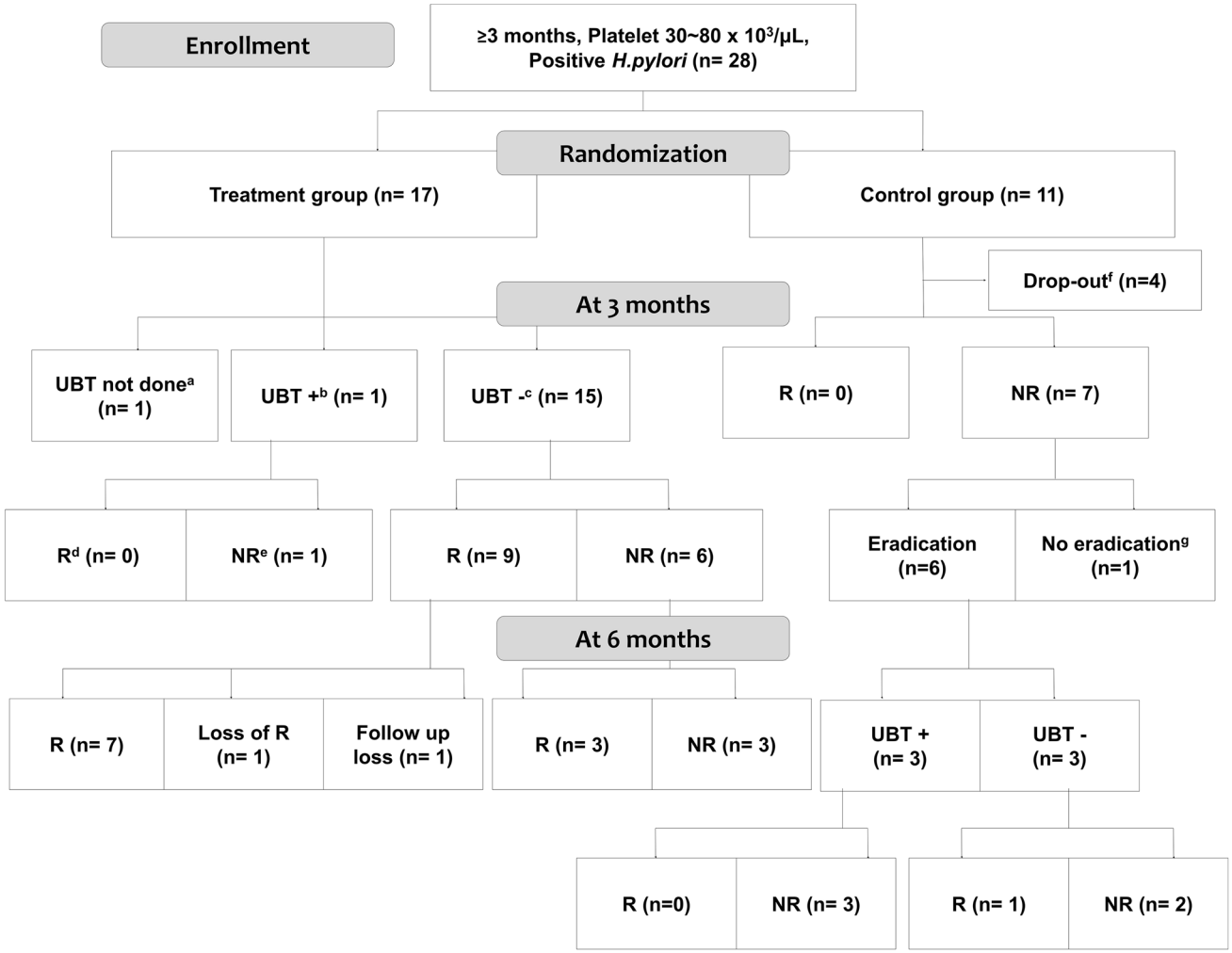

Fig. 1 Study consort diagram. The platelet response rate at 3 months as the primary endpoint was 60% for the treatment group with successful eradication and 0% for the control group ($p = 0.017$). [a]Urea breath test (UBT) not done: At the time of treatment initiation after the screening, one patient experienced decrease of platelet count to less than 30×10^3/μL. Hence, we terminated this study process after follow-up up to 2 months where the patient did not undergo the follow-up UBT. [b]UBT+: failure of *H. pylori* eradication. [c]UBT-: success of *H. pylor*i eradication. [d]R: platelet response. [e]NR: no platelet response. [f]Drop-out: Patient who withdrew from the study after randomization. [g]No eradication: At 2 months, the platelet count was 98×10^3/μL. The study was terminated at the discretion of the investigator

randomization group (Table 3). All nine patients in the platelet responder group were treated for *H. pylori*. The platelet non-responder group included seven participants in the treatment group and seven in the control group. There were no significant differences in age, baseline platelet count, prevalence period after ITP diagnosis, or previous ITP treatment history between the two groups. However, the proportion of women in the platelet non-responder group was significantly higher at 85.7%. In 100% of subjects of the platelet responder group, UBT was negative at 3 months of follow-up, confirming the success of *H. pylori* eradication. In the platelet non-responder group, only 42.9% of subjects were found to be UBT negative, significantly ($p = 0.005$) lower than in the platelet responder group. In the multivariate analysis, success or failure of *H. pylori* eradication was the only independent predictor of platelet response at 3 months after eradication (HR 0.4, 95% CI 0.006–0.794, $p = 0.047$). We conducted similar analysis in 15 patients who achieved successful eradication where no statistically significant differences in clinical characteristics between the platelet responders and non-responders were seen.

Discussion

According to existing treatment guidelines, when there is no bleeding and the platelet count is 30×10^3/μL or more, patients with ITP can only be examined regularly without

Table 1 Baseline characteristics of the study population[a]

		Treatment group ($n=17$)		Control group[c] ($n=7$)
		All patients ($n=17$)	Successfully eradicated patients[b] ($n=15$)	
Age (year) (median [IQR[d]])		58.00 [49.00, 64.00]	53.00 [44.50, 63.50]	53.00 [46.00, 63.50]
Sex (male:female)		7:10	5:10	1:6
Months from diagnosis to enrollment (median [IQR])		17.80 [3.30, 56.40]	21.50 [7.45, 59.00]	18.10 [7.10, 30.20]
Previous treatment (yes)[e]		3 (17.6%)	3 (20%)	2 (28.6%)
Alcohol consumption (Yes)		4 (23.5%)	3 (20%)	1 (14.3%)
Baseline platelet counts, $\times 10^3$/μL (median [IQR])		56.00 [46.00, 59.00]	56.00 [46.00, 59.00]	51.00 [50.00, 72.50]
Baseline platelet counts	$30\sim50\times10^3$/μL	7 (41.2%)	6 (40.0%)	1 (14.3%)
	$50\sim80\times10^3$/μL	10 (58.8%)	9 (60.0%)	6 (85.7%)
MPV[f] (fL) (median [IQR])		11.00 [10.60, 11.90]	11.20 [10.75, 11.98]	11.30 [10.60, 11.78]
PDW[g] (fL) (median [IQR])		13.80 [12.60, 16.80]	13.65 [12.52, 16.42]	14.10 [12.60, 14.70]
Hemorrhagic symptom score (median [IQR])		1.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.50]
Hemoglobin (g/dL) (median [IQR])		13.80 [13.00, 15.40]	13.80 [13.05, 15.00]	13.20 [12.80, 13.60]
WBC[h] counts (/μL) (median [IQR])		5900.00 [4750.00, 6900.00]	5900.00 [4735.00, 6805.00]	5060.00 [4125.00, 7030.00]
Neutrophil count (/μL) (median [IQR])		3355.00 [2620.00, 3729.00]	3355.00 [2711.00, 3643.00]	2798.00 [2239.50, 4137.00]
Creatinine (mg/dL) (median [IQR])		0.80 [0.65, 0.95]	0.70 [0.60, 0.80]	0.70 [0.70, 0.80]
BUN[i](mg/dL) (median [IQR])		14.00 [13.10, 17.25]	14.00 [12.20, 15.00]	13.20 [11.30, 14.00]
AST[j] (IU/L) (median [IQR])		25.00 [19.50, 31.00]	20.00 [19.00, 28.00]	20.00 [19.00, 24.50]
ALT[k] (IU/L) (median [IQR])		26.00 [16.00, 31.50]	18.00 [16.00, 31.00]	19.00 [16.00, 20.00]
Total bilirubin (mg/dL) (median [IQR])		0.90 [0.70, 1.00]	0.90 [0.80, 1.00]	1.00 [0.55, 1.15]

[a]All clinical features showed no statistical significance between the treatment group and the control group, and between the treatment group with successful eradication and the control group

[b]Successfully eradicated patients in the treatment group: Refers to patients with UBT negative conversion among all treatment groups

[c]In the control group, four patients who were dropped out were excluded in the analysis of baseline characteristics

[d]*IQR* interquartile range

[e]Two received corticosteroid and intravenous immunoglobulin, other three received intravenous immunoglobulin, eltrombopag, danazol monotherapy, respectively

[f]*MPV* mean platelet volume

[g]*PDW* platelet distribution width

[h]WBC: white blood cell

[i]BUN: blood urea nitrogen

[j]AST: aspartate aminotransferase

[k]ALT: alanine aminotransferase

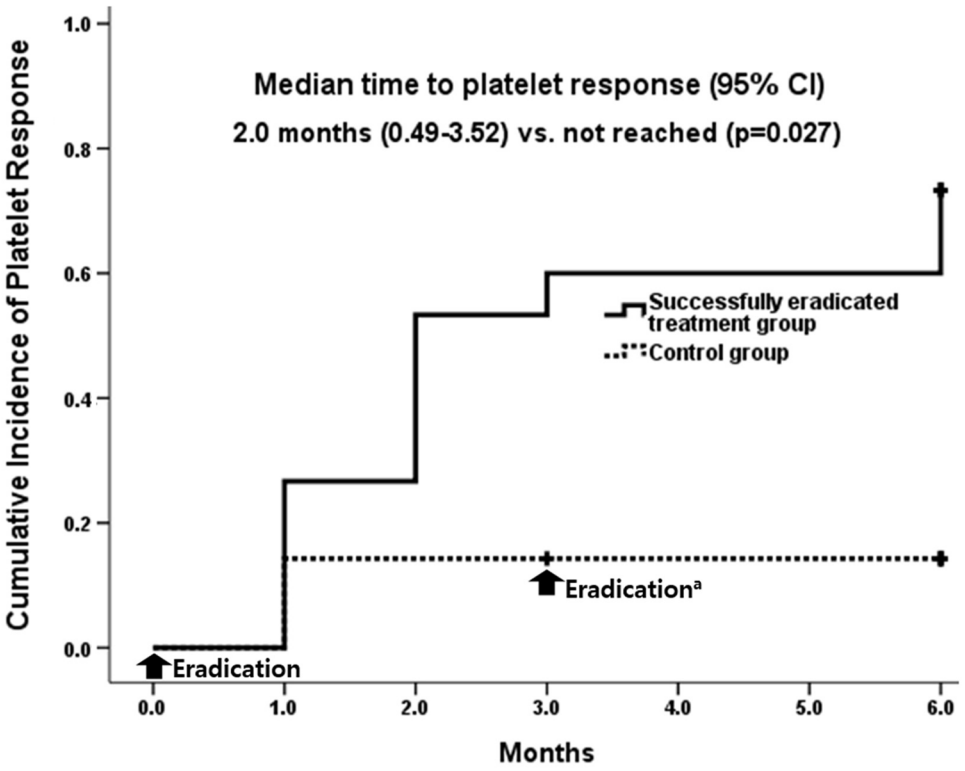

Fig. 2 Time to platelet response after *H*. pylori eradication *pylori* eradication. The median time to platelet response was 2 months (95% CI, 0.49–3.52 months) in patients with successful eradication among treatment groups. One subject in the control group showed platelet response at 1 month that was lost at 3 months and regained it at 6 months (the time of 3 months after eradication). [a]*H. pylori* eradication treatment was performed for the control group at 3 months. Gray's test for was used

Table 2 Toxicities observed during the treatment period

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	1	3	0	0
Epigastric soreness	1	0	0	0
Palpitation	1	0	0	0
Diarrhea	1	0	0	0

Toxicity grade was evaluated according to NCI-CTCAE, version 4.0

All patients who took the eradication treatment drug for more than 1 day were investigated. The evaluation was performed for 17 patients in the treatment group and six patients in the control group who underwent eradication treatment at 3 months

any specific management. This is due to treatment-related adverse effects, the possibility of long-term treatment, and the financial burden of treatment such as corticosteroid, IVIG, splenectomy, thrombopoietin agonist, and rituximab. As a result, ITP patients with moderate thrombocytopenia who were not indicated for the treatment are continuously exposed to bleeding risks, even if they are not at high risk.

For ITP patients with confirmed *H. pylori* infection, eradication may be considered as a treatment option. Based on clinical experiences, several studies have attempted to elucidate the mechanism of *H. pylori*-related ITP. Hypotheses presented so far include the molecular mimicry hypothesis stating that anti-CagA antibodies against *H. pylori* can cross-react with platelet surface antigen [27], autoreactivity expression of T cells and B cells as a response of the host immune system after *H. pylori* infection [28], and the pathogenic hypothesis stating that the platelet autoantibody continues to respond by modulating monocyte/macrophage function as a result of this autoimmune response [29]. However, the mechanism cannot be fully explained by one factor. A multi-factorial mechanism might be involved [30].

In particular, *H. pylori* has been pointed out as a cause of benign diseases such as atrophic gastritis, intestinal metaplasia, peptic ulcer disease, malignant tumors such as gastric cancer and mucosa-associated lymphoid tissue lymphoma, and ITP. For this reason, guidelines in Korea and Japan known to have a high prevalence of *H. pylori* recommend eradication treatment when *H. pylori* infection is diagnosed in ITP patients with mild or moderate severity [31, 32].

The evidence of eradication as a treatment of ITP has been proven based on the previous studies showing platelet responses after *H. pylori* eradication in ITP patients. However, in most of these studies, the target patient group was not homogeneous, and *H. pylori* eradication was commonly combined with other ITP treatments such as steroids [10–15, 33]. Therefore, we conducted a phase 2 study with standard 3-drug treatment enrolling only a group of ITP patients with moderate thrombocytopenia who had not been treated in the past [16]. In this study, the overall response rate was 57.7% at 3 months of treatment and 30.8% at 12 months of treatment. Most (87.5%) responders showed complete responses. This confirms an effective and durable response with relatively few side effects. However, recent studies on *H. pylori*

Table 3 Comparison of clinical characteristics between treatment responders and non-responders at 3 months after *H. pylori* eradication

		PLT responder[a] ($n=9$)	PLT non-responder[b] ($n=7+7$)	p value
Age (year) (median [IQR[c]])		53.00 [28.00, 64.00]	55.50 [49.25, 63.00]	0.825
Sex (male:female)		5:4 (55.6%:44.4%)	2:12 (14.3%:85.7%)	0.036 (0.104)[d]
Months from diagnosis to enrollment (median [IQR])		21.53 [7.43, 74.40]	15.55 [0.69, 45.24]	0.485
Months from diagnosis to enrollment	Chronic ($\geq$ 12 months)	6 (66.7%)	9 (64.3%)	0.907
	Non-chronic (< 12 months)	3 (33.3%)	5 (35.7%)	
Previous treatment	No	8 (88.9%)	10 (71.4%)	0.322
	Yes	1 (11.1%)	4 (28.6%)	
Baseline platelet counts, $\times 10^3/\mu L$ (median [IQR])		58.00 [56.00, 59.00]	50.00 [46.00, 70.00]	0.549
Baseline platelet counts	$30 \sim 50 \times 10^3/\mu L$	1 (11.1%)	6 (42.9%)	0.106
	$50 \sim 80 \times 10^3/\mu L$	8 (88.9%)	8 (57.1%)	
Baselines MPV[e] (median [IQR])		11.45 [10.97, 11.98]	10.80 [10.35, 11.65]	0.264
Baselines PDW[f] (median [IQR])		13.50 [12.45, 15.60]	14.25 [13.20, 16.42]	0.641
UBT[g] results	Negative	9 (100.0%)	6 (42.9%)	0.005 (0.047)[d]
	Positive	0 (0.0%)	8 (57.1%)	
Platelet counts at 3 months, $\times 10^3/\mu L$ (median [IQR])		135.00 [108.00 152.00]	64.0 [42.00 76.75]	< 0.001

[a]Platelet (PLT) responder: nine patients in the treatment group who showed a platelet response at 3 months

[b]PLT non-responder: Patients who did not show a platelet response at 3 months (seven participants in the treatment group and seven in the control group) were combined

[c]*IQR* interquartile range

[d]*p* value in multivariate analysis

[e]*MPV* mean platelet volume

[f]*PDW* platelet distribution width

[g]*UBT* urea breath test

eradication have reported that the eradication rate of the existing standard 3-drug treatment is less than 70% due to drug resistance [18, 19]. Sequential eradication treatment to overcome this problem has been proposed, and an excellent eradication rate of about 80% has been reported [21–24]. Considering drug resistance, this study attempted a sequential treatment rather than the standard 3-drug treatment and determined whether appropriate platelet response could be obtained with this new treatment. To the best of our knowledge, this is the first study to conduct a sequential *H. pylori* eradication monotherapy, multicenter, phase 3, randomized study in patients with moderate thrombocytopenia only.

In this study, the *H. pylori* eradication rate at 3 months was 88.2% for patients who received the sequential eradication treatment. This percentage was higher than those reported in recent studies using a standard 3-drug treatment. This sequential eradication treatment showed excellent drug compliance without causing significant toxicity. Besides, the final platelet response rate of 60% was similar to those reported after the conventional 3-drug treatment [10–15]. Therefore, the use of sequential eradication treatment might be expected to have an increasing effect on platelet responders for ITP patients compared to the existing 3-drug treatment. Besides, considering the association between *H. pylori* and other diseases, choosing a treatment regimen with a high eradication rate for *H. pylori*-positive ITP patients not only can improve platelet response, but also can prevent other *H. pylori*-related diseases including lymphoma and gastric cancer. The higher eradication rate of the sequential treatment used in this study is helpful for the prevention and symptom improvement of *H. pylori*-induced other diseases by itself. Since the drug price is relatively inexpensive, such treatment can be said to be ideal.

This study did not evaluate long-term response for more than 12 months as per the authors' previous phase 2 study. However, at 3 months and 6 months, it was confirmed that

the total platelet response rate was steadily maintained at 60% or more. Besides, six patients in the control group who did not have a platelet response at 3 months were subjected to the same eradication afterwards. Their median platelet counts also tended to increase at 6 months. To confirm the effect of bleeding symptom improvement in these patients, the median difference of the hemorrhagic symptom score with IQR between before and after treatment was also analyzed and observed to be improved in patients in the successfully eradicated treatment group compared to those in the control group. However, this finding was thought to be due to a minor bleeding event in one patient in the control group, and clinically significant bleeding did not occur in both groups of patients. After the diagnosis of ITP in patients participating in this study, the median prevalence period until they were enrolled in this study was 17.9 months (IQR, 3.1–52.7 months). About 20% of these patients had a history of using treatments including steroids before. Therefore, the results of the present study suggest that eradication treatment alone can produce an excellent response, regardless of the prevalence duration or past ITP treatment history.

A previous study suggested that some platelet improvement after eradication treatment in *H. pylori*-positive ITP patients might be due to other reasons rather than by the eradication, including an immune modulating effect by antibiotic therapy itself or by eradication of other commensal bacteria [34]. However, the fact that platelet response was observed in patients who achieved successful *H. pylori* eradication even when the eradication regimen was changed as shown in this study suggested that the eradication success itself was related to the improvement of platelet count, and not because of specific antibiotics. This has also been reported in a retrospective study analysis of more than 100 patients [35].

In this study, factors predicting platelet response were evaluated. Univariate analysis revealed that the platelet response was decreased in women (Table 3). However, the multivariate analysis did not show a statistically significant difference in platelet response between males and females. This might be due to a high proportion of women in the total patient group and the control group. The result that there was no difference in treatment effect according to sex was consistent with several previous studies that observed platelet response after ITP treatment including *H. pylori* eradication [36–44].

In contrast to results of study in Asian countries such as Korea and Japan, several previous studies conducted in other regions were not significantly superior, with platelet responses of 7–30%, after *H. pylori* eradication treatment [40, 45–49], and a meta-analysis has shown similar results [6]. The influence of ethnic differences and heterogeneity of the study participants can be considered as the cause of such difference. Ethnic differences in *H. pylori* species and differences in *H. pylori* prevalence have been reported in several studies [50, 51]. The genetic diversity of *H. pylori* strains may be the reason for such *H. pylori* prevalence difference and ethnic differences in platelet response after eradication. Besides, when geographical grouping was performed through bacterial sequencing, a pattern similar to racial distribution according to human migration that has been hypothesized and explained [52]. For this reason, *H. pylori* detection and eradication in areas with high prevalence and virulence are very reasonable and scientific approach for patients with ITP. In particular, when applying a treatment, it is necessary to select an appropriate treatment in consideration of *H. pylori* prevalence, ethnic differences of strains, and differences in resistance to antibiotics by region. International studies are needed in the future to clarify existing hypotheses about ethnicity differences of *H. pylori*'s prevalence, virulence, and ITP treatment response.

Several studies in which platelet response is poor after eradication mentioned above, the therapeutic effect of *H. pylori* eradication might have been underestimated due to heterogeneous inclusion of ITP patients with moderate and severe thrombocytopenia, a study design allowing treatment with steroids in the control group. Therefore, in *H. pylori* eradication studies, a study design that selects more homogenous ITP patients is needed to help determine the effectiveness of the eradication treatment.

However, in this study, indication of *H. pylori* eradication for ITP patients was changed due to extended insurance coverage in Korea. Therefore, the study was terminated early because an ethical problem could arise if the treatment is delayed for the control group. Due to this, the total number of enrolled patients was smaller than planned. Besides, because our study was non-blind, four patients in the control group withdrew from the study post- randomization after recognizing their assignment. This was another limitation of our study in terms of small sample size. However, results of this study still showed a positive effect of the sequential eradication treatment with a statistical significance.

Conclusion

This study confirmed that a sequential eradication treatment was effective and tolerable in *H. pylori*-positive ITP patients with moderate thrombocytopenia. Therefore, this might give justification for the evaluation of *H. pylori* infection and eradication in the *H. pylori*-positive ITP patients with mild to moderate thrombocytopenia, currently recommended only for follow-up without treatment. In addition, the sequential treatment could be considered as a standard eradication regimen for *H. pylori*-positive ITP, especially in the areas where drug resistance is increasing.

Acknowledgements Additionally, we thank Nayoung Kim (Department of Internal Medicine, Seoul National University Bundang Hospital, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine) for helping the development of the sequential treatment regimen used in this study.

Author contribution Hyo Jung Kim, Hwa Jung Kim, and Soo-Mee Bang designed the study concept; Boram Han, Hyo Jung Kim, Ho-Young Yhim, Doyeun Oh, Sung Hwa Bae, Ho-Jin Shin, Won-Sik Lee, JiHyun Kwon, Jeong-Ok Lee, and Soo-Mee Bang performed the study; Boram Han, Hyo Jung Kim, and Hwa Jung Kim analyzed the study; Boram Han wrote the manuscript; Hyo Jung Kim and Soo-Mee Bang critically reviewed the study; Boram Han and Hyo Jung Kim contributed equally to this work.

Funding This work was supported by a grant (13–2017-016) from the SNUBH Research Fund.

Data availability Members of the research designed the trial and protocol, collected the data, met to oversee the trial, and wrote the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Declarations

Ethics approval The trial was conducted in accordance with the revised Helsinki guidelines. The study protocol was approved by institutional review boards in the participating institutions.

Competing interest The authors declare no competing interests.

References

1. Cines DB, Blanchette VS (2002) Immune thrombocytopenic purpura. N Engl J Med 346:995–1008. https://doi.org/10.1056/NEJMra010501
2. Barsam SJ, Psaila B, Forestier M, Page LK, Sloane PA, Geyer JT, Villarica GO, Ruisi MM, Gernsheimer TB, Beer JH, Bussel JB (2011) Platelet production and platelet destruction: assessing mechanisms of treatment effect in immune thrombocytopenia. Blood 117:5723–5732. https://doi.org/10.1182/blood-2010-11-321398
3. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N, Godeau B, Lechner K, Mazzucconi MG, McMillan R, Sanz MA, Imbach P, Blanchette V, Kühne T, Ruggeri M, George JN (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 113:2386–2393. https://doi.org/10.1182/blood-2008-07-162503
4. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 117:4190–4207. https://doi.org/10.1182/blood-2010-08-302984
5. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G (1998) Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. Lancet 352:878. https://doi.org/10.1016/S0140-6736(05)60004-9
6. Stasi R, Sarpatwari A, Segal JB, Osborn J, Evangelista ML, Cooper N, Provan D, Newland A, Amadori S, Bussel JB (2009) Effects of eradication of Helicobacter pylori infection in patients with immune thrombocytopenic purpura: a systematic review. Blood 113:1231–1240. https://doi.org/10.1182/blood-2008-07-167155
7. Franchini M, Cruciani M, Mengoli C, Pizzolo G, Veneri D (2007) Effect of Helicobacter pylori eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. J Antimicrob Chemother 60:237–246. https://doi.org/10.1093/jac/dkm195
8. Jackson S, Beck PL, Pineo GF, Poon MC (2005) Helicobacter pylori eradication: novel therapy for immune thrombocytopenic purpura? A review of the literature. Am J Hematol 78:142–150. https://doi.org/10.1002/ajh.20250
9. Arnold DM, Bernotas A, Nazi I, Stasi R, Kuwana M, Liu Y, Kelton JG, Crowther MA (2009) Platelet count response to *H. pylori* treatment in patients with immune thrombocytopenic purpura with and without *H. pylori* infection: a systematic review. Haematologica 94(6):850–856
10. Suzuki T, Matsushima M, Masui A, Watanabe K, Takagi A, Ogawa Y, Shirai T, Mine T (2005) Effect of Helicobacter pylori eradication in patients with chronic idiopathic thrombocytopenic purpura-a randomized controlled trial. Am J Gastroenterol 100:1265–1270. https://doi.org/10.1111/j.1572-0241.2005.41641.x
11. Tsutsumi Y, Kanamori H, Yamato H, Ehira N, Kawamura T, Umehara S, Mori A, Obara S, Ogura N, Tanaka J, Asaka M, Imamura M, Masauzi N (2005) Randomized study of Helicobacter pylori eradication therapy and proton pump inhibitor monotherapy for idiopathic thrombocytopenic purpura. Ann Hematol 84:807–811. https://doi.org/10.1007/s00277-005-1071-z
12. Li CX, Liu DJ, Pan CQ, Sang XF, Li X (2009) Effect of Helicobacter pylori eradication on childhood acute idiopathic thrombocytopenic purpura. Nan Fang Yi Ke Da Xue Xue Bao 29:1243–1244
13. Treepongkaruna S, Sirachainan N, Kanjanapongkul S, Winaichatsak A, Sirithorn S, Sumritsopak R, Chuansumrit A (2009) Absence of platelet recovery following Helicobacter pylori eradication in childhood chronic idiopathic thrombocytopenic purpura: a multi-center randomized controlled trial. Pediatr Blood Cancer 53:72–77. https://doi.org/10.1002/pbc.21991
14. Tang Y, Wang SC, Wang LJ, Liu Y, Wang HY, Wang ZJ (2013) Clinical significance of Helicobacter pylori in children with idiopathic thrombocytopenic purpura. Zhongguo Shi Yan Xue Ye Xue Za Zhi 21:419–421. https://doi.org/10.7534/j.issn.1009-2137.2013.02.033
15. Brito HSH, Braga JAP, Loggetto SR, Machado RS, Granato CFH, Kawakami E (2015) Helicobacter pyloriinfection & immune thrombocytopenic purpura in children and adolescents: a randomized controlled trial. Platelets 26:336–341. https://doi.org/10.3109/09537104.2014.911836
16. Kim H, Lee WS, Lee KH, Bae SH, Kim MK, Joo YD, Zang DY, Jo JC, Lee SM, Lee JH, Lee JH, Kim DY, Ryoo HM, Hyun MS, Kim HJ, CoOperative Study Group A for Hematology (COSAH) (2015) Efficacy of Helicobacter pylori eradication for the 1st line treatment of immune thrombocytopenia patients with moderate thrombocytopenia. Ann Hematol 94:739–746. https://doi.org/10.1007/s00277-014-2268-9
17. Kim N, Kim JJ, Choe YH, Kim HS, Kim JI, Chung IS, Korean College of Helicobacter and Upper Gastrointestinal Research, Korean Association of Gastroenterology (2009) Diagnosis and treatment guidelines for Helicobacter pylori infection in Korea. Korean J Gastroenterol 54:269–278. https://doi.org/10.4166/kjg.2009.54.5.269
18. Lee JY, Kim N, Kim MS, Choi YJ, Lee JW, Yoon H, Shin CM, Park YS, Lee DH, Jung HC (2014) Factors affecting first-line triple therapy of Helicobacter pylori including CYP2C19 genotype and antibiotic resistance. Dig Dis Sci 59:1235–1243. https://doi.org/10.1007/s10620-014-3093-7

19. Boyanova L, Mitov I (2010) Geographic map and evolution of primary Helicobacter pylori resistance to antibacterial agents. Expert Rev Anti-Infect Ther 8:59–70. https://doi.org/10.1586/eri.09.113
20. Oh HS, Lee DH, Seo JY, Cho YR, Kim N, Jeoung SH, Kim JW, Hwang JH, Park YS, Lee SH, Shin CM, Cho HJ, Jung HC, Song IS (2012) Ten-day sequential therapy is more effective than proton pump inhibitor-based therapy in Korea: a prospective, randomized study. J Gastroenterol Hepatol 27:504–509. https://doi.org/10.1111/j.1440-1746.2011.06922.x
21. Wu DC, Hsu PI, Wu JY, Opekun AR, Kuo CH, Wu IC, Wang SSW, Chen A, Hung WC, Graham DY (2010) Sequential and concomitant therapy with four drugs is equally effective for eradication of H pylori infection. Clin Gastroenterol Hepatol 8:36-41. e1. https://doi.org/10.1016/j.cgh.2009.09.030
22. Yoon K, Kim N (2019) Eradication rates of 10-day sequential therapy for Helicobacter pylori: results of an 8-year prospective study conducted at a tertiary Korean hospital. Korean J Gastroenterol 73:99–104. https://doi.org/10.4166/kjg.2019.73.2.99
23. Scaccianoce G, Hassan C, Panarese A, Piglionica D, Morini S, Zullo A (2006) Helicobacter pylori eradication with either 7-day or 10-day triple therapies, and with a 10-day sequential regimen. Can J Gastroenterol 20:113–117. https://doi.org/10.1155/2006/258768
24. Zullo A, De Francesco V, Hassan C, Morini S, Vaira D (2007) The sequential therapy regimen for Helicobacter pylori eradication: a pooled-data analysis. Gut 56:1353–1357. https://doi.org/10.1136/gut.2007.125658
25. Yoon H, Lee DH, Kim N, Park YS, Shin CM, Kang KK, Oh DH, Jang DK, Chung JW (2013) Meta-analysis: is sequential therapy superior to standard triple therapy for Helicobacter pylori infection in Asian adults? J Gastroenterol Hepatol 28:1801–1809. https://doi.org/10.1111/jgh.12397
26 George JN, el-Harake MA, Raskob GE (1994) Chronic idiopathic thrombocytopenic purpura. N Engl J Med 331:1207–1211. https://doi.org/10.1056/NEJM199411033311807
27. Michel M, Khellaf M, Desforges L, Lee K, Schaeffer A, Godeau B, Bierling P (2002) Autoimmune thrombocytopenic purpura and Helicobacter pylori infection. Arch Intern Med 162:1033–1036. https://doi.org/10.1001/archinte.162.9.1033
28. Yamanishi S, Iizumi T, Watanabe E, Shimizu M, Kamiya S, Nagata K, Kumagai Y, Fukunaga Y, Takahashi H (2006) Implications for induction of autoimmunity via activation of B-1 cells by Helicobacter pylori urease. Infect Immun 74:248–256. https://doi.org/10.1128/IAI.74.1.248-256.2006
29. Kuwana M, Okazaki Y, Ikeda Y (2009) Splenic macrophages maintain the anti-platelet autoimmune response via uptake of opsonized platelets in patients with immune thrombocytopenic purpura. J Thromb Haemost 7:322–329. https://doi.org/10.1111/j.1538-7836.2008.03161.x
30. Kuwana M (2014) Helicobacter pylori-associated immune thrombocytopenia: clinical features and pathogenic mechanisms. World J Gastroenterol 20:714–723. https://doi.org/10.3748/wjg.v20.i3.714
31. Jung HK, Kang SJ, Lee YC, Yang HJ, Park SY, Shin CM, Kim SE, Lim HC, Kim JH, Nam SY, Shin WG, Park JM, Choi IJ, Kim JG, Choi M, Korean College of Helicobacter and Upper Gastrointestinal Research (2021) Evidence based guidelines for the treatment of Helicobacter pylori infection in Korea 2020. Korean J Intern Med 36:807–838. https://doi.org/10.3904/kjim.2020.701
32. Kato M, Ota H, Okuda M, Kikuchi S, Satoh K, Shimoyama T, Suzuki H, Handa O, Furuta T, Mabe K, Murakami K, Sugiyama T, Uemura N, Takahashi S (2019) Guidelines for the management of Helicobacter pylori infection in Japan: 2016, revised edition. Helicobacter 24(4):e12597. https://doi.org/10.1111/hel.12597
33. Lee A, Hong J, Chung H, Koh Y, Cho SJ, Byun JM, Kim SG, Kim I (2020) Helicobacter pylori eradication affects platelet count recovery in immune thrombocytopenia. Sci Rep 10:9370. https://doi.org/10.1038/s41598-020-66460-5
34. Ianaro A, Ialenti A, Maffia P, Sautebin L, Rombolà L, Carnuccio R, Iuvone T, D'Acquisto F, Di Rosa MD (2000) Anti-inflammatory activity of macrolide antibiotics. J Pharmacol Exp Ther 292:156–163
35. Hwang JJ, Lee DH, Yoon H, Shin CM, Park YS, Kim N (2016) The effects of Helicobacter pylori eradication therapy for chronic idiopathic thrombocytopenic purpura. Gut Liver 10:356–361. https://doi.org/10.5009/gnl14483
36. Daou S, Federici L, Zimmer J, Maloisel F, Serraj K, Andrès E (2008) Idiopathic thrombocytopenic purpura in elderly patients: a study of 47 cases from a single reference center. Eur J Intern Med 19:447–451. https://doi.org/10.1016/j.ejim.2007.07.006
37. Ando K, Shimamoto T, Tauchi T, Ito Y, Kuriyama Y, Gotoh A, Miyazawa K, Kimura Y, Kawai T, Ohyashiki K (2003) Can eradication therapy for Helicobacter pylori really improve the thrombocytopenia in idiopathic thrombocytopenic purpura? Our experience and a literature review. Int J Hematol 77:239–244. https://doi.org/10.1007/BF02983780
38. Sato R, Murakami K, Watanabe K, Okimoto T, Miyajima H, Ogata M, Ohtsuka E, Kodama M, Saburi Y, Fujioka T, Nasu M (2004) Effect of Helicobacter pylori eradication on platelet recovery in patients with chronic idiopathic thrombocytopenic purpura. Arch Intern Med 164:1904–1907. https://doi.org/10.1001/archinte.164.17.1904
39. Inaba T, Mizuno M, Take S, Suwaki K, Honda T, Kawai K, Fujita M, Tamura T, Yokota K, Oguma K, Okada H, Shiratori Y (2005) Eradication of Helicobacter pylori increases platelet count in patients with idiopathic thrombocytopenic purpura in Japan. Eur J Clin Invest 35:214–219. https://doi.org/10.1111/j.1365-2362.2005.01471.x
40. Stasi R, Rossi Z, Stipa E, Amadori S, Newland AC, Provan D (2005) Helicobacter pylori eradication in the management of patients with idiopathic thrombocytopenic purpura. Am J Med 118:414–419. https://doi.org/10.1016/j.amjmed.2004.09.014
41. Fujimura K, Kuwana M, Kurata Y, Imamura M, Harada H, Sakamaki H, Teramura M, Koda K, Nomura S, Sugihara S, Shimomura T, Fujimoto TT, Oyashiki K, Ikeda Y (2005) Is eradication therapy useful as the first line of treatment in Helicobacter pylori-positive idiopathic thrombocytopenic purpura? Analysis of 207 eradicated chronic ITP cases in Japan. Int J Hematol 81:162–168. https://doi.org/10.1532/ijh97.04146
42. Kodama M, Kitadai Y, Ito M, Kai H, Masuda H, Tanaka S, Yoshihara M, Fujimura K, Chayama K (2007) Immune response to CagA protein is associated with improved platelet count after Helicobacter pylori eradication in patients with idiopathic thrombocytopenic purpura. Helicobacter 12:36–42. https://doi.org/10.1111/j.1523-5378.2007.00477.x
43. Satake M, Nishikawa J, Fukagawa Y, Akashi K, Okamoto T, Yoshida T, Hirano A, Maetani N, Iida Y, Sakaida I (2007) The long-term efficacy of Helicobacter pylori eradication therapy in patients with idiopathic thrombocytopenic purpura. J Gastroenterol Hepatol 22:2233–2237. https://doi.org/10.1111/j.1440-1746.2007.04845.x
44. Emilia G, Luppi M, Zucchini P, Morselli M, Potenza L, Forghieri F, Volzone F, Jovic G, Leonardi G, Donelli A, Torelli G (2007) Helicobacter pylori infection and chronic immune thrombocytopenic purpura: long-term results of bacterium eradication and association with bacterium virulence profiles. Blood 110:3833–3841. https://doi.org/10.1182/blood-2006-12-063222
45. Jarque I, Andreu R, Llopis I, De la Rubia JD, Gomis F, Senent L, Jiménez C, Martín G, Martínez JA, Sanz GF, Ponce J, Sanz MA (2001) Absence of platelet response after eradication of Helicobacter pylori infection in patients with chronic idiopathic

thrombocytopenic purpura. Br J Haematol 115:1002–1003. https://doi.org/10.1046/j.1365-2141.2001.03194.x
46. Michel M, Cooper N, Jean C, Frissora C, Bussel JB (2004) Does Helicobacter pylori initiate or perpetuate immune thrombocytopenic purpura? Blood 103:890–896. https://doi.org/10.1182/blood-2003-03-0900
47. Suvajdzić N, Stanković B, Artiko V, Cvejić T, Bulat V, Bakrac M, Colović M, Obradović V, Atkinson HDE (2006) Helicobacter pylori eradication can induce platelet recovery in chronic idiopathic thrombocytopenic purpura. Platelets 17:227–230. https://doi.org/10.1080/09537100500462487
48. Ahn ER, Tiede MP, Jy W, Bidot CJ, Fontana V, Ahn YS (2006) Platelet activation in Helicobacter pylori-associated idiopathic thrombocytopenic purpura: eradication reduces platelet activation but seldom improves platelet counts. Acta Haematol 116:19–24. https://doi.org/10.1159/000092343
49. Estrada-Gómez RA, Parra-Ortega I, Martínez-Barreda C, Ruiz-Argüelles GJ (2007) Helicobacter pylori infection and thrombocytopenia: a single-institution experience in Mexico. Rev Invest Clin 59:112–115
50. O'Neill CM, Weitz IC, O'Connell C, Liebman HA (2019) Ethnic and racial difference in Helicobacter pylori infection in patients with immune thrombocytopenia treated at a major urban medical center. Platelets 30:413–417. https://doi.org/10.1080/09537104.2018.1453061
51. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC (2017) Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology 153:420–429. https://doi.org/10.1053/j.gastro.2017.04.022
52. Linz B, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, Falush D, Stamer C, Prugnolle F, van der Merwe SW, Yamaoka Y, Graham DY, Perez-Trallero E, Wadstrom T, Suerbaum S, Achtman M (2007) An African origin for the intimate association between humans and Helicobacter pylori. Nature 445:915–918. https://doi.org/10.1038/nature05562

Authors and Affiliations

Boram Han[1] · Hyo Jung Kim[1] · Ho-Young Yhim[2] · Doyeun Oh[3] · Sung Hwa Bae[4] · Ho-Jin Shin[5] · Won-Sik Lee[6] · JiHyun Kwon[7] · Jeong-Ok Lee[8] · Hwa Jung Kim[9,10] · Soo-Mee Bang[8]

1 Division of Hematology-Oncology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea

2 Division of Hematology-Oncology, Department of Internal Medicine, Jeonbuk National University Medical School, Jeonju, Republic of Korea

3 Division of Hematology-Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea

4 Division of Hematology-Oncology, Department of Internal Medicine, Daegu Catholic University Hospital, Daegu, Republic of Korea

5 Division of Hematology-Oncology, Department of Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea

6 Division of Hematology-Oncology, Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Republic of Korea

7 Division of Hematology-Oncology, Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Republic of Korea

8 Division of Hemato-Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea

9 Department of Prevention Medicine, University of Ulsan College of Medicine, Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, Republic of Korea

10 Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, Republic of Korea