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ORIGINAL ARTICLE

Efficacy of *Helicobacter pylori* eradication for the 1st line treatment of immune thrombocytopenia patients with moderate thrombocytopenia

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Abstract The practical usefulness of *Helicobacter pylori* eradication for immune thrombocytopenia (ITP) patients is still controversial. However, some ITP patients respond to *H. pylori* eradication. We conducted a multi-center, open label, prospective phase II study to define the efficacy and toxicities of *H. pylori* eradication as the first line treatment for persistent or chronic ITP patients with moderate thrombocytopenia. Patients with persistent or chronic ITP showing moderate thrombocytopenia (30×10^9/L≤platelet count≤70×10^9/L) and positive C^{13}-urea breath test (UBT) were selected. Medication consisted of lansoprazole 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg orally twice daily for a week. Complete response (CR) rate at 4 weeks, 3 months, 6 months, 12 months, and maximal response was 19.2, 50.0, 50.0, 26.9, and 65.4 %, respectively. Overall response rate (ORR) at 4 weeks, 3 months, 6 months, 12 months, and maximal response was 19.2, 57.7, 65.4, 30.8, and 69.2 %, respectively. Median maximal platelet count during the first 3 months was 110×10^9/L (range, 40–274). Median time to CR was 8 weeks (95 % CI=5.429–10.571). Median time to ORR was 4 weeks (95 % CI=1.228–6.772). Only per-protocol population was a response predictor for ORR at 3 months (70.0 %, p=0.054) and maximal ORR (80.0 %, p=0.051), but not for CR at 3 months (60.0 %, p=0.160). Therefore, eradication of *H. pylori* is an effective and durable first line treatment for persistent or chronic ITP with moderate thrombocytopenia with high ORR and rapid onset in this study.

Keywords Helicobacter pylori · Immune thrombocytopenia · Eradication

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Introduction

Current treatment guideline of ITP recommends corticosteroid as the first line treatment when patient has active bleeding or less than 30×10^9/L of platelet, because of side effect and cost issues. Since the first case report by Gasbarrini et al., several investigators have reported that secondary immune thrombocytopenia (ITP) can occur in patients with *Helicobacter pylori* (*H. pylori*) infection [6, 9]. Eradication of *H. pylori* has been shown to improve thrombocytopenia [4, 6]. In one systematic review of 696 patients with *H. pylori* infection, overall response (platelet count$\geq30\times10^9$/L and at least a doubling of the base line count) after *H. pylori* eradication was 50.3 % [14]. Under these results, ASH 2011 guidelines for ITP recommended that eradication therapy could be administered in adult patients who have *H. pylori* infection (grade 1b) [2]. ASH 2011 guidelines also recommended that the eradication treatment for newly diagnosed patients with a platelet count$<30\times10^9$/L. There are some practical needs for elevating platelet counts in moderate ITP patients if the treatment is effective. We hypothesized that minimal risk treatment would be beneficial for moderate ITP patients. To the best of our knowledge, there was no prospective study that has evaluated the efficacy of *H. pylori* eradication for ITP patients with moderate thrombocytopenia and positive *H. pylori*. In Korea, the prevalence of *H. pylori* was reported to be as high as 60–65 % in general adult population. The response rate to first line triple regimen for *H. pylori* eradication was known to be 70–80 %. However, the price of medication is around 100 US dollars in Korea. With these circumstances, tolerable treatment like *H. pylori* eradication for ITP patients with platelet count$\geq30\times10^9$/L is challengeable. Thus, we performed the prospective study to evaluate the efficacy of *H. pylori* eradication for the first line treatment of persistent or chronic ITP patients with moderate thrombocytopenia (ClinicalTrials.gov: NCT01255332; COSAH-023).

Patients and methods

Study design

This was a multi-center, open label, prospective phase II study to define the efficacy and toxicities of *H. pylori* eradication as the first line treatment for persistent or chronic ITP patients with moderate thrombocytopenia. The primary end point was an overall response rate (ORR) at 3 months after treatment. This study was approved by each participating institutional review board and ethic committee. All procedures were in accordance with the Helsinki Declaration. Informed consent was obtained from all patients for being included in the study.

Patients

Inclusion criteria were 20–60 years old persistent or chronic ITP patients defined by international working group [13]; 30×10^9/L$\leq$platelet count$\leq70\times10^9$/L; positive C^{13}-urea breath test (UBT); no previous ITP treatment; no previous *H. pylori* eradication treatment; and patients with informed consents indicating that they were aware of the investigational nature of the study according to the policy of the hospital. Exclusion criteria were patients who had any cause of thrombocytopenia such as HIV, HCV infection, lymphoproliferative disease, liver disease, definite SLE, drug, MDS, and leukemia; uncontrolled hypothyroidism or hyperthyroidism; acute active bleeding or infection; patients who were taking anticoagulant or aspirin; patients with penicillin allergy or side effects of macrolide; patients who were taking mizolastine, terfenadien, cisapride, pimozide, astemizole, ergot alkaloid and its derivatives (ergotamine and dihydroergotamine), bepridil, or atazanavir; patients who had known allergy or severe side effect on study drugs; pregnant or lactating women; and clinically relevant hepatic or renal disease (creatinine clearance$\leq$30 mL/min). We assessed the severity of hemorrhagic symptoms at the time of study enrollment with clinical hemorrhage scoring system (HSS) [7].

Treatment and evaluation

All patients were assigned to take study medication for a week. The study medication consisted of lansoprazole 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg orally twice daily. Eradication of *H. pylori* was evaluated at eighth week after treatment by UBT. Platelet counts were monitored at 2 weeks after treatment. After that, platelet counts were monitored every month for a year.

Criteria for assessing response to treatment were defined by international working group [13]. Quality of response was defined as complete response (CR) when platelets count was $\geq100\times10^9$/L in the absence of bleeding; or responsive (R) when platelets count was $\geq30\times10^9$/L with increases of at least twofold from the baseline count without bleeding; or no response (NR) when platelet count was $<30\times10^9$/L or there was less than twofold increase from baseline platelet count or there was any evidence of bleeding caused by thrombocytopenia. Time to response was defined as duration from starting treatment to the time of achieving CR or R. Loss of CR or R was designated when platelet count was below 100×10^9/L or bleeding (from CR) or below 30×10^9/L or less than twofold increase of baseline platelet count or bleeding (from R). Duration of response was measured from the achievement of CR or R to the date of losing CR or R. When a response was not evaluable at certain time point, the response was designated as no response (NR).

The intent-to-treat (ITT) population was defined as patients assigned to a treatment group who would receive *H. pylori* eradication therapy without considering protocol eligibility. For efficacy analysis, ITT was the primary analysis population. Modified ITT (mITT) population was defined as evaluable patients among ITT population in terms of response at each time point. The per-protocol (PP) population was defined as the group of patients who received at least one dose of treatment without protocol deviations (e.g., ineligibility and missing assessments). Patients older than 55 years but less than 60 years were included in PP population after protocol revision. Patients excluded from the PP population were identified prior to a database lock. For efficacy analysis, mITT and PP were secondary analysis population. Safety population was defined as all patients assigned to a treatment group who receive at least one dose of study drug. The primary analysis population was ITT unless there was a population is specified. Demographics and baseline characteristics were analyzed using the ITT population. All efficacy endpoints were analyzed in ITT, PP, and mITT populations. Safety endpoints were analyzed using the safety population.

Statistical considerations

Primary end point was ORR, which was defined as CR+R at 3 months after treatment. Secondary end points were time to response, duration of response, side effect, safety of treatment, and eradication rate of *H. pylori*. Planned number of subjects was 21 under the assumption of P0=20 %, P1=50 %, α=0.05, and β=0.1. Therefore, we planned enrolling a total of 26 patients to this study considering 25 % drop out rate. Demographic data were summarized as median, standard deviation, maximum, and minimum for continuous variables. For categorical variables, data were summarized in tables of frequencies and percentages. Response rate with 95 % confidence interval was calculated. Time to response and response duration were analyzed by Kaplan–Meyer method. Clinical predictors were analyzed by χ^2. Correlation relationship was identified by Pearson correlation and linear regression. Statistical significance was considered when p value was less than 0.05 %.

Results

Study enrollment and performance

A total of 26 patients were recruited to this study between November 2010 and May 2013 from six medical centers in Korea. These patients were ITT population (Fig. 1). Among them, six were excluded from PP population, including two patients for being HCVAb(+); one for HBsAg(+); one for history of prior ITP therapy; one for initial platelet count> 70×10^9/L; and one for ITP diagnosed within 3 months. Therefore, 20 patients were included in the PP population. All patients except one completed *H. pylori* eradication therapy. However, the patient had to stop the medication due to nausea. Therefore, all ITT populations were included in safety population. Two patients from the PP population could not be evaluated for response at 4 weeks. The remaining 24 patients were included in the mITT population at 4 weeks. All 24 patients were available for response evaluation at 3 months. They were included in the mITT population at 3 months. Another five patients in PP population and two patients in protocol violation group were lost to follow up evaluation at 6 months. The number of the mITT population at 12 months was 16 after one patient was lost to follow up after 6 months in the PP population.

Patients' characteristics

Females (n=18, 69.2 %) were more frequent than male (n=8, 30.8 %). Median age was 44.5 years (range, 19–58) (Table 1). Seventeen patients had bone marrow biopsy with normal results although it was not an essential diagnostic procedure. All patients met inclusion criterion for positive UBT. There was no positive HIV or anti-nuclear antibody titer. Two patients showed HBsAg(+) at screening test, one of them was excluded from the PP population, the other one was HBsAb(+) in the PP population. Most patients (n=21, 80.8 %) scored 0 on HSS. Initial platelet count of one patient was 38×10^9/L scored 4 on HSS. Median duration from ITP diagnosis to study enrollment was 4.2 months (range, 0.2–91.5). Median WBC, hemoglobin, and platelet count at study enrollment were 6325×10^6/L (range, 1180–9600), 13.6 g/dL (range, 11.3\–16.7), and 53.5×10^9/L (range, 39–77), respectively.

H. pylori eradication

Adverse events were found in only 2 of 26 patients. One of them didn't complete full schedule of medications for *H. pylori* eradication due to grade 3 nausea. The other patient experienced grade 1 diarrhea but completed medications. There was no other significant adverse event. Follow-up UBT after 8 weeks of *H. pylori* eradication was available in 25/26 patients. All patients in PP population obtained follow-up UBT results. The rate of *H. pylori* eradication was 80.0 % (20/25 in ITT and 16/20 in PP population). The patient who didn't complete *H. pylori* eradication remained positive in follow-up UBT. Four patients who had not achieved *H. pylori* negative conversion received second trial. However, two of them still showed positive UBT.

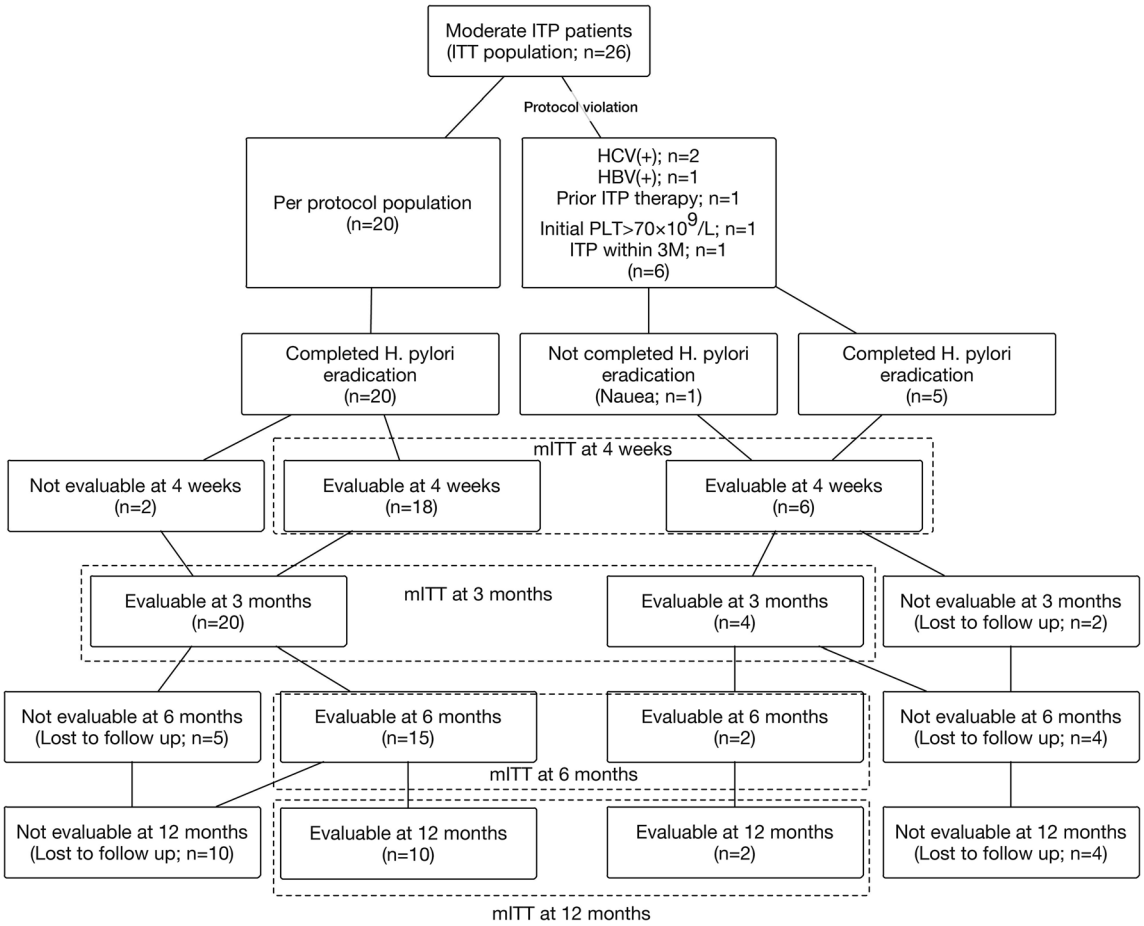

Fig. 1 Definition of study populations and enrollment of patients. *ITP* immune thrombocytopenia; *ITT* intent-to-treat; *HCV* anti-hepatitis C antibody; *HBV* hepatitis B surface antigen; *PLT* platelet; *mITT* modified intent-to-treat population

Platelet response to *H. pylori* eradication

As shown in Table 2, CR rates at 4 weeks, 3 months, 6 months, 12 months, and maximal response were 19.2, 50.0, 50.0, 26.9, and 65.4 %, respectively. ORR at 4 weeks, 3 months, 6 months, 12 months, and maximal response was 19.2, 57.7, 65.4, 30.8, and 69.2 %, respectively. Median maximal platelet counts during the first 3 months were 110×10^9/L (range, 40–274). Median time to CR was 8 weeks (95 % CI=5.429–10.571) (Fig. 2a). Median time to CR or R was 4 weeks (95 % CI=1.228–6.772) (Fig. 2b).

When the analysis was confined to PP population, CR rates at 4 weeks, 3 months, 6 months, 12 months, and maximal response were 20.0, 60.0, 60.0, 35.0, and 75.0 %, respectively. ORR at 4 weeks, 3 months, 6 months, 12 months, and maximal response in PP population was 20.0, 70.0, 75.0, 40.0, and 80.0 %, respectively. Median times to CR and CR/R in PP population were 8 (95 % CI=5.723–10.277) and 4 weeks (95 % CI=1.387–6.613), respectively (Fig. 2c, d). Response evaluation among evaluable patients was performed in the mITT population. CR rates at 4 weeks, 3 months, 6 months, 12 months, and maximal response in the mITT population were 20.8, 54.2, 52.9, 58.3, and 65.4 %, respectively. ORR at 4 weeks, 3 months, 6 months, 12 months, and maximal response in the mITT population was 20.8, 62.5, 76.5, 66.7, and 69.2 %, respectively.

Predictor for response to *H. pylori* eradication

Age, gender, initial platelet count, initial WBC count, initial hemoglobin, PP population, ITP duration, anti-nuclear antibody, LDH, anti-HBV antibody, anti-HCV antibody, and follow-up UBT were tested to predict variables for platelet response to *H. pylori* eradication in terms of CR at 3 months, ORR at 3 months, and maximal ORR (Table 3). Only PP population was a response predictor for ORR at 3 months (70.0 %, $p=0.054$) and maximal ORR (80.0 %, $p=0.051$), but not for CR at 3 months (60.0 %, $p=0.160$). Similar results were taken when the analysis was confined to PP population (data not shown). UBT negative conversion at 4 weeks later was not a predicting factor for responses. There was only marginal significance for maximal ORR (14/16, $p=0.162$) in PP population. There was no correlation between initial platelet count and maximal platelet count (Pearson correlation=−0.052; $r^2=0.003$, $p=0.801$, Fig. 3).

Table 1 Characteristics of patients

Characteristics	No. of patients	(%)
Gender, Male	8	(30.8)
Bone marrow biopsy	17	(65.4)
UBT, Positive	26	(100)
Prior ITP treatment	1	(3.8)
Hemorrhagic symptoms and score		
0	21	(80.8)
1	4	(15.4)
4	1	(3.8)
HBsAg, Positive	2	(7.7)
HCVAb, Positive	2	(7.7)
	Median	(Range)
Age, years	44.5	(19–58)
Weeks since diagnosis	18.4	(1–398)
Initial blood counts		
WBC, $\times 10^6$/L	6325	(1180–9600)
Hemoglobin, g/dL	13.6	(11.3–16.7)
Platelet, $\times 10^9$/L	53.5	(39–77)

UBT C^{13} -urea breath test; *ITP* immune thrombocytopenia; *HBsAg* Hepatitis B surface antigen; *HCVAb* anti-hepatitis C antibody

Follow-up results

Twelve patients remained in follow-up at 12 months, whereas 14 patients were lost to follow up. Median duration of follow-up was 11.6 months (range, 0.7–30.4) in the ITT population and 13.2 months (range, 3.19–30.4) in the PP population. Two patients lost their responses after achieving CR, including one HCVAb(+) patient who lost CR to no response at 48 weeks and one patient in the PP population who lost CR to R at 40 weeks. No patient showed decline of platelet count to below 3×10^9/L which would need regular ITP therapy.

Discussion

Is there a need for treating ITP patients with moderate thrombocytopenia? Many guidelines and review articles do not recommend treating non-symptomatic or moderate thrombocytopenia with more than 30×10^9/L platelet count, unless there is a significant bleeding or accident or surgery [1, 8, 10–12]. However, some patients were anxious about observing low platelet count without treatment, even though their platelet count was more than 30×10^9/L which is known by patients to be usually safe with very low probability of thrombocytopenic bleeding risk. Some patients were concerned about occupational restriction, bleeding risk by accident, and emergency surgery. If there is an effective, safe, and cheap therapy, there is no reason to hesitate on the treatment to correct a certain abnormality. In countries with high prevalence of *H. pylori* infection and high platelet count response rates following eradication, testing for *H. pylori* infection has been recommended as a standard diagnostic procedure in adults with ITP. Ideally, treatments for ITP should be effective, safe, tolerable, and inexpensive. Detection and eradication of *H. pylori* infection is safe, tolerable, and inexpensive. However, its effectiveness has not been consistent. Whether simple *H. pylori* eradication could elevate platelet count in moderate ITP patients was unknown. Therefore, this study aimed to answer these questions.

One patient who had a prior history of ITP therapy was evaluated in this study in the ITT population. Prior ITP

Table 2 Platelet response to *H. pylori* eradication therapy

Time point	Response	ITT	mITT	PP
4 weeks	CR	5/26 (19.2 %)	5/24 (20.8 %)	4/20 (20.0 %)
	R	0/26 (0.0 %)	0/24 (0.0 %)	0/20 (0.0 %)
	ORR	5/26 (19.2 %)	5/24 (20.8 %)	4/20 (20.0 %)
3 months	CR	13/26 (50.0 %)	13/24 (54.2 %)	12/20 (60.0 %)
	R	2/26 (7.7 %)	2/24 (8.3 %)	2/20 (10.0 %)
	ORR	9/26 (57.7 %)	15/24 (62.5 %)	14/20 (70.0 %)
6 months	CR	13/26 (50.0 %)	9/17 (52.9 %)	12/20 (60.0 %)
	R	4/26 (15.4 %)	4/17 (23.5 %)	3/20 (15.0 %)
	ORR	17/26 (65.4 %)	13/17 (76.5 %)	15/20 (75.0 %)
12 months	CR	7/26 (26.9 %)	7/12 (58.3 %)	7/20 (35.0 %)
	R	1/26 (3.8 %)	1/12 (8.3 %)	1/20 (5.0 %)
	ORR	8/26 (30.8 %)	8/12 (66.7 %)	8/20 (40.0 %)
Maximal response	CR	17/26 (65.4 %)	17/26 (65.4 %)	15/20 (75.0 %)
	R	1/26 (3.8 %)	1/26 (3.8 %)	1/20 (5.0 %)
	ORR	18/26 (69.2 %)	18/26 (69.2 %)	16/20 (80.0 %)

ITT intent-to treat population; *mITT* modified intent-to treat population; *PP* per-protocol population; *CR* complete response; *R* responsive; *ORR* overall response rate (CR+R)

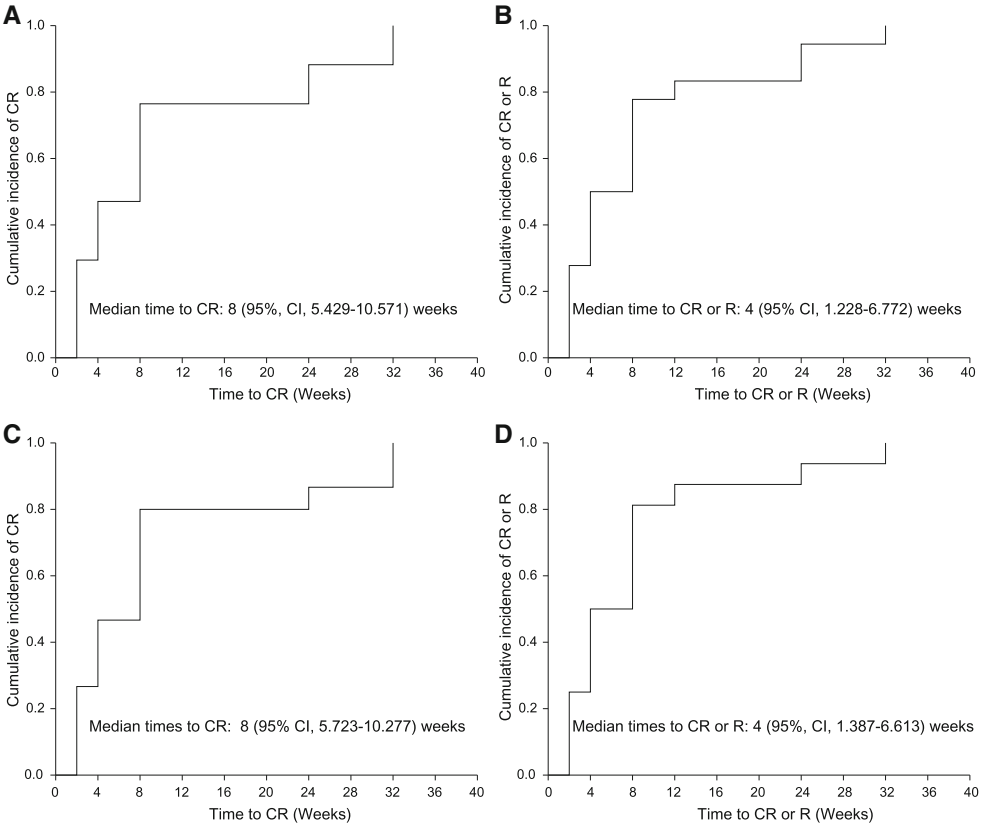

Fig. 2 Time to platelet response after *H. pylori* eradication therapy. Median times to response for responders were plotted in intent-to treat population (**a** and **b**) and in per-protocol population (**c** and **d**). Time to complete response (CR) was shown in **a** and **b**. Time to overall response rate (CR+R) was shown in **b** and **c**

therapy included splenectomy and steroid therapy. Therefore, *H. pylori* eradication might become a salvage regimen for a certain proportion of patients who are refractory or have relapsed from the first line therapy. To confirm this concept, a prospective clinical trial of *H. pylori* eradication for salvage therapy in ITP is merited. A secondary cause could happen in approximately 20 % of ITP patients [2]. This percentage could be greater in parts of the world where predisposing infections such as *H. pylori* are endemic. Percentage of secondary cause in ITP is likely to grow as new etiologies are elucidated [3]. After the relationship between *H. pylori* infection and ITP was first described 10 years ago by Gasbarrini et al. [6] many

Table 3 Clinical predictors for platelet response at 3 months after *H. pylori* eradication therapy

Variables	CR at 3 M		ORR at 3 M		Maximal ORR	
	No. Patients (%)	*p* value	No. of patients (%)	*p* value	No. of patients (%)	*p* value
Age<45 years	6/13 (46.2 %)	0.695	8/13 (61.5 %)	0.691	10/13 (76.9 %)	0.673
Gender, male	3/8 (37.5 %)	0.678	4/8 (50.0 %)	0.683	4/8 (50.0 %)	0.197
Initial platelet<50×10^9/L	3/7 (42.9 %)	1.000	5/7 (71.8 %)	0.658	6/7 (85.7 %)	0.375
Initial WBC<6300×10^6/L	5/12 (41.7 %)	0.431	6/12 (50.0 %)	0.462	8/12 (66.7 %)	1.000
Initial Hb<13 g/dL	4/10 (40.0 %)	0.668	5/10 (50.0 %)	0.689	6/10 (60.0 %)	0.664
PP population	12/20 (60.0 %)	0.160	14/20 (70.0 %)	0.054	16/20 (80.0 %)	0.051
ITP duration<4 M	7/12 (58.3 %)	0.431	7/12 (58.3 %)	0.951	8/12 (66.7 %)	1.000
ANA(+)	1/3 (33.3 %)	1.000	1/3 (33.3 %)	0.556	2/3 (66.7 %)	1.000
LDH<220 IU/L	4/9 (44.4 %)	0.287	5/9 (55.6 %)	0.508	7/9 (77.8 %)	1.000
HBsAb(+)	5/9 (55.6 %)	1.000	5/9 (55.6 %)	1.000	6/9 (62.7 %)	1.000
HCVAb(−)	13/24 (54.2 %)	0.480	15/24 (62.5 %)	0.169	17/24 (70.8 %)	0.529
Follow-up UBT(−)	11/20 (55.0 %)	0.646	12/20 (60.0 %)	1.000	15/20 (83.3 %)	0.330

CR complete response; *ORR* overall response rate (CR+R); *Hb* hemoglobin; *PP* per-protocol; *ITP* immune thrombocytopenia; *ANA* anti-nuclear antibody; *HBsAb* anti-Hepatitis B surface antibody; *HCVAb* anti-hepatitis C antibody; *UBT* C^{13} -urea breath test

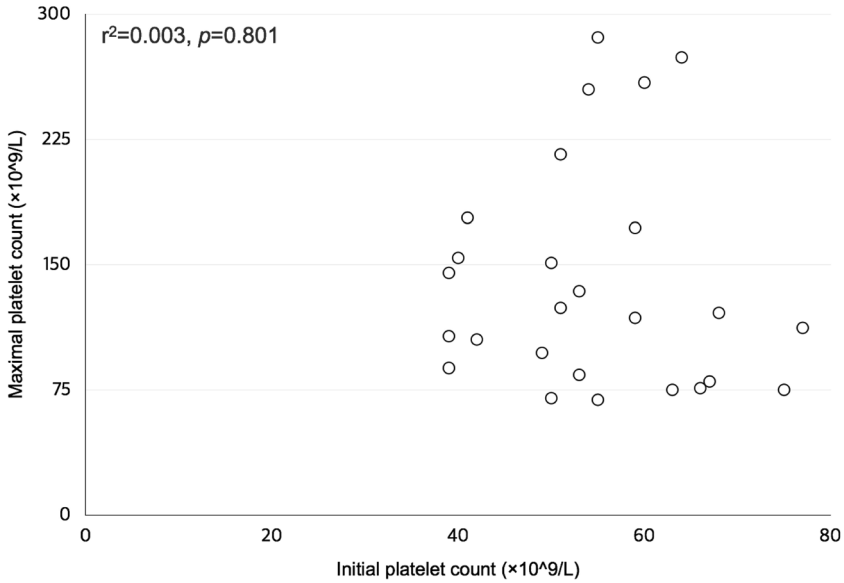

Fig. 3 Correlation between initial platelet count and maximal platelet count

hypotheses were proposed as the mechanism of *H. pylori*-induced thrombocytopenia. A molecular mimicry existed between *H. pylori*-induced antibodies and various platelet glycoprotein antigens that can cross-react with *H. pylori*-induced antibodies [15]. CagA, a virulence factor of *H. pylori*, can induce production of antibodies that could cross-react with a peptide specifically expressed by platelets of patients with ITP [15].

A systematic literature review conducted by Stasi et al. including 1555 patients showed an overall response was observed in 50 % of the cases [14]. These results are compatible with the current study. Our median time to ORR was 4 weeks. This result was compatible with a report by Stasi et al., in which response occurred most commonly 2 weeks after completing eradication therapy.

Our results showed no correlation between ORR and successful *H. pylori* eradication. On the contrary, Fujimura et al. reported that in 207 *H. pylori*-positive ITP cases, the platelet count response was observed in 63 % of the successful eradication group and in 33 % of the unsuccessful eradication group ($p<0.005$) [5]. Therefore, the correlation between successful eradication and response should be studied further. Of the four patients received second trial of *H. pylori* eradication, three achieved CR, although two of them were still positive in follow-up UBT. This suggest that if a follow-up UBT is still positive after the first *H. pylori* eradication trial without response until 4 weeks, the second trial can be helpful for increasing platelet count even though it may not eradicate *H. pylori* at all.

Our ORR at 3 months was 57.7 %. ORR was as high as 70 % in the PP population. Stasi's report showed an ORR of 50 %. When reducing the analysis to patients with a baseline platelet count $\leq 30\times10^9$/L, the ORR was only 35 %, [14] suggesting that *H. pylori* eradication could be more effective in moderate thrombocytopenia patients along with our current results. This could mean that there was more *H. pylori*-related ITP in moderate thrombocytopenia than severe thrombocytopenia. Only the PP population was a response predictor for ORR at 3 months (70.0 %, $p=0.054$) and maximal ORR (80.0 %, $p=0.051$), suggesting that well-designed criteria for *H. pylori* eradication might be able to increase the response in moderate ITP. However, there was no correlation between initial platelet count and maximal platelet count ($r^2=0.003$, $p=0.801$). ORR was not correlated with initial platelet count. Therefore, *H. pylori* eradication might be useful for ITP patients with moderate thrombocytopenia, regardless of platelet count. This assumption should be confirmed by further studies.

The response rates were much higher in countries where the rate of *H. pylori* carriage is high [14]. Many ITP patients are associated with *H. pylori* infection in *H. pylori* endemic area if other secondary causes are excluded. This concept can be supported by that the only relevant clinical predictor for platelet response to *H. pylori* eradication was the PP population, although it was not statistically significant. Therefore, much more ITP patients might be able to respond to *H. pylori* eradication when adequate inclusion criteria are applied. Our result of much higher ORR than other trials could be due to the fact that Korea is a *H. pylori* endemic region [16].

Loss of response was observed in only two patients among 18 responders, suggesting that the effect of *H. pylori* eradication on platelet recovery was sustainable and that *H. pylori* eradication therapy could be used as a first line therapy even in moderate thrombocytopenia patients who are not candidates for therapy in usual guidelines. The purpose of this study was not to verify the relationship between *H. pylori* and ITP, but to determine whether *H. pylori* eradication could elevate platelet count in patients with moderate ITP. Therefore, the results of this

study do not provide direct evidence that *H. pylori* is a causative agent of ITP. The long-term sustainability of *H. pylori* eradication should be confirmed by further long-term follow-up.

The number of patients in this study is quite small. We designed this study according to the expected first 3-month response rate after *H. pylori* eradication. Therefore, the primary end point was response rate at 3 months. The number of patients was adequate as a phase II study when considering meta-analysis data. Our calculation showed that 21 patients were enough to confirm our speculation. Therefore, we enrolled 26 patients after considering a 25 % drop out rate. Our result was evaluating responses according to intention-to-treat. All 20 patients were evaluable, even for per-protocol population analysis. Therefore, the number of patients of this study for a phase II study was adequate to confirm our speculation. However, this small study could not be used to confirm the efficacy of *H. pylori* eradication in moderate ITP patients. Another limitation of this study is the possibility of spontaneous remission. To minimize the possibility of spontaneous remission in ITP patients, we enrolled patients with low possibility of spontaneous remission: persistent or chronic ITP. The definition of persistent or chronic ITP was based on international working group [13]. However, we cannot exclude the possibility that some responders could spontaneously recover not necessarily by *H. pylori* eradication. Therefore, a phase III trial is needed to confirm the result of this study.

In summary, the eradication therapy of *H. pylori* is an effective first line treatment for persistent or chronic ITP with moderate thrombocytopenia with high ORR, rapid onset, and durable response. The eradication therapy has acceptable toxicity and relatively low cost. This study supports a routine detection and eradication of *H. pylori* infection in ITP patients, especially in populations with a high prevalence of *H. pylori* infection.

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Author contribution HJK designed study concept; HK, WSL, KHL, SHB, MKK, JCJ, JHL, JHL, DYK, SML, HMR, MSH and HJK performed study; HK wrote the manuscript; YDJ and HJK critically reviewed study. HK and WSL contributed equally to this work.

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