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Effect of *Helicobacter pylori* infection on the first-line treatment outcomes in patients with immune thrombocytopenic purpura

A. DOGAN[1], O. EKINCI[2], S. EBINC[3]

[1]Department of Hematology, Faculty of Medicine, Yüzüncü Yil University, Van, Turkey
[2]Istinye University Bahcesehir LIV Hospital, Hematology Unit, Istanbul, Turkey
[3]Department of Medical Oncology, Faculty of Medicine, Dicle University, Diyarbakir, Turkey

Abstract. – OBJECTIVE: *Helicobacter pylori* (*H. pylori*) eradication therapy is known to increase the platelet count, but in immune thrombocytopenic purpura (ITP), the effect of *H. pylori* infection on the response to treatment is not clear. This study aims to determine whether the response to the first-line treatment is affected by the states of *H. pylori*-positivity and -negativity in ITP patients.

PATIENTS AND METHODS: Adult newly diagnosed or chronic ITP patients who had not received eradication therapy for *H. pylori* infection were included. Characteristics of the patients, presence and severity of bleeding, initial platelet count, administered treatments, and treatment response rates were inspected.

RESULTS: Of 119 total patients, 66 (55.5%) were female, 32 (26.9%) were *H. pylori*-positive, 87 (73.1%) were *H. pylori*-negative. *H. pylori*-positive and *H. pylori*-negative groups were not significantly different in terms of age (p=0.127), gender (p=0.078), diagnosis status (p=0.094) and the distribution of bleeding symptoms (p=0.712). The most common treatment was standard-dose steroid in both groups (62.5% *vs.* 68.9%, p=0.524). Rates of complete response, partial response, no response were comparable for the two groups (respectively, 75% *vs.* 73.6%, and 18.8% *vs.* 19.5%, and 6.2% *vs.* 6.9%), and there was no significant difference between the groups (p=0.283).

CONCLUSIONS: It can be stated, according to the present study, that in ITP patients in whom treatment is indicated, the response to the first-line treatment without the administration of *H. pylori* eradication therapy is similar between *H. pylori*-positive and *H. pylori*-negative patients.

Key Words:
Helicobacter pylori, Immune thrombocytopenic purpura, First-line treatment.

Introduction

Immune (idiopathic) thrombocytopenic purpura (ITP) is an acquired disease characterized by a temporary or permanent decrease in the platelet count that results from the effects of immune–mediated anti–platelet antibodies[1]. Its prevalence in adults is approximately 5–10/100.000 and it is more common among females in the adult age group[2]. It is usually associated with a chronic progression and an elevated risk of bleeding due to the severity of thrombocytopenia[3].

Thrombocytopenia may be induced by antibodies that are produced in response to pathogen antigens and cross-react with platelets in certain infections. These antibodies mainly occur in viral infections but also consist of bacterial infections. There is no mechanism that has been proposed to explain how *Helicobacter pylori* (*H. pylori*) could be involved in the pathogenesis of immune–mediated platelet destruction. However, the role of bacterial factors such as the cytotoxin–associated gene A (CagA) protein is currently being investigated[4]. Particularly, lipopolysaccharides in bacteria are reported to bind to the platelet membrane and trigger platelet phagocytosis similarly[5].

The relationship between *H. pylori* infection and ITP was first defined in 1998 by Gasbarrini et al[6] in a study where they reported a high platelet count in 8 of their 11 ITP patients. Since then, numerous studies on *H. pylori* eradication in ITP have been published. However, it is still controversial whether *H. pylori* eradication always increases the platelet count in patients diagnosed with ITP. Comprehensive reviews suggest that eradication therapy would need to be considered if a *H. pylori* infection is detected in patients with typical ITP[7]. Studies in the literature have generally focused on the effects of the eradication of *H. pylori* infection on increasing the platelet count in ITP patients. The effects of *H. pylori* positivity on the response to the standard first-line ITP treatment are not clear. The present study aims to determine whether or not the response to the first-line treatment is

Corresponding Author: Ali Dogan, MD; e-mail: dr.alidogan44@gmail.com

affected by *H. pylori*-positive and -negative states in patients diagnosed with ITP.

Patients and Methods

Patients

A retrospective study in adult patients who were either newly diagnosed with ITP or were under follow-up for chronic ITP at Yüzüncü Yıl University Hospital, Van, Turkey was conducted from January 2010 to March 2019. In this single-centered study, the follow-up records and data of the patients in the hospital system were retrospectively evaluated. Inclusion criteria included: having a diagnosis of ITP, being older than 18 years, treatment indication and having undergone treatment for ITP, and for those with a *H. pylori*-positive test result, not having received eradication therapy. Patients who were younger than 18 years, were never treated for ITP, underwent eradication therapy, had missing data were excluded from the study. There is a standardized antibiotic therapy for the eradication of *H. pylori* in our hospital. In this treatment, lansoprazole (30 mg/day PO), amoxicillin (1000 mg PO, q 12 h), clarithromycin (500 mg PO, q 12 h) and bismuth subsalicylate (524 mg PO, q 12 h) are given for 14 days.

The diagnosis of ITP was confirmed according to the Consensus Report on the Investigation and Management of Primary ITP[7]. Patients were categorized into two groups: *H. pylori*-positive and -negative. Fecal antigen testing was used for the diagnosis of *H. pylori* infection in all patients. Demographic data of the patients at diagnosis, presence and severity of bleeding, initial platelet count, administered treatments, treatment response rates, and post–treatment platelet count were inspected. The incoming blood sample for complete blood count (CBC) was studied by the "Advia 2120i System with Autoslide-Healthineers, Germany" brand device.

The study was approved by the Research Ethics Committee of Yuzuncu Yil University, Faculty of Medicine (date/reference number: 24.01.2018/002). All analyses were performed in accordance with the principles of the Declaration of Helsinki.

Categorization of Bleeding Symptoms

The bleeding symptoms were evaluated according to the International Working Group (IWG) bleeding scale. In this scale, bleeding manifestations are grouped into three major domains: skin (S), visible mucosae (M), and organs (O), with a gradation of severity (SMOG). The patients were graded based on physical examination at the time of the visit or on the patient's history and medical reports. The severity of bleeding, as defined in this scale, was graded from 0 to 4[8].

Evaluation of Response After First-Line Treatment

Response rates were categorized as complete response, partial response, or no response as follows: a platelet count lower than 30×10^9/L and absence of doubling from baseline was considered as no response; a platelet count $\geq30\times10^9$/L but $<100\times10^9$/L, and presence of a doubling from baseline and absence of bleeding were considered as a partial response; and a platelet count $\geq100\times10^9$/L that persisted for 3 months or longer was considered as a complete response[1].

Statistical Analysis

Statistical analysis of the data was performed using the IBM SPSS 22 (SPSS Inc., IBM, Armonk, NY, USA) statistical package program. Descriptive statistics for studied variables (characteristics) were presented as mean, standard deviation, median, minimum and maximum values, and for categorical variables the frequency is expressed as a percentage [n (%)]. For determining the relationship between groups and categorical variables, the Chi-square test was used. In order to compare *H. pylori*-positive and *H. pylori*-negative groups for demographic, clinical and laboratory characteristics, the Man-Whitney U test were performed. The level of significance was set at $p < 0.05$.

Results

Patients' Characteristics

Of the 119 total patients included in the study, 66 (55.5%) were female. At diagnosis, 32 patients (26.9%) were *H. pylori*-positive and 87 (73.1%) were *H. pylori*-negative. The *H. pylori*-positive and *H. pylori*–negative groups showed a similar median age (32 *vs.* 34) and gender distribution (F/M: 18/14 *vs.* 48/39), with no statistically significant difference in these regards (respectively, p=0.127 and p=0.078). Both groups predominantly consisted of newly diagnosed patients and were not significantly different in this aspect [28(87.5%) *vs.* 80(91.9%), p=0.094]. Demographic, clinical and laboratory characteristics of patients with *H. pylori*-positive and *H. pylori*-negative ITP were shown in Table I.

Table I. Demographic, clinical and laboratory characteristics of patients with ITP.

Characteristics	*H. pylori*-positive (N=32)	*H. pylori*-negative (N=87)	*p*-value
Age, year			0.127
Median	32	34	
Range	18-68	18-63	
Sex, n (%)			0.078
Female	18 (56.3)	48 (55.2)	
Male	14 (43.7)	39 (44.8)	
Diagnosis status, n (%)			0.094
Newly diagnosis	28 (87.5)	80 (91.9)	
Chronic ITP	4 (12.5)	7 (8.1)	
Baseline platelet count, $\times 10^9$/L			0.354
Mean ± SD	18.4±22.3	19.5±21.8	
Median (range)	12 (3–28)	14 (2–30)	
Bleeding symptoms, n (%)			0.712
Grade 0	7 (21.8)	18 (20.7)	
Grade 1	18 (56.3)	47 (54.1)	
Grade 2	5 (15.6)	16 (18.3)	
Grade 3	2 (6.3)	5 (5.8)	
Grade 4	0	1 (1.1)	

Bleeding Symptoms and Platelet Counts

The mean platelet count was determined as 18.4±22.3 × 10^9/L for the *H. pylori*–positive patient group and as 19.5±21.8×10^9/L for the *H. pylori*-negative patient group; and these groups were not significantly different in terms of platelet count (p=0.354). Bleeding categories according to the IGW scale were also not significantly different across these groups, with grade 1 bleeding being the most common grade in both groups (for grade 1 bleeding; 56.3% *vs.* 54.1%, for all grades p=0.712) (Table I).

First-Line Treatment Option and Response Rates

First-line treatment options and response rates of patients with *H. pylori*–positive and *H. pylori*–negative ITP were shown in Table II. First-line treatment options offered to all ITP patients were as follows: standard–dose steroid or standard–dose steroid plus IVIG or high–dose steroid or high–dose steroid plus IVIG. The most common form of treatment was standard–dose steroid (62.5% *vs.* 68.9%) in both groups and the groups were not different with regard to treatment options (p=0.524). Rates of complete response, partial response, and no response after first-line treatment were comparable for the two groups (respectively, 75% *vs.* 73.6%, and 18.8% *vs.* 19.5%, and 6.2% *vs.* 6.9%) and there was no significant difference between the groups (p=0.283). Median platelet count after first-line treatment was determined as 214×10^9/L for *H. pylori*–positive patients and as 242×10^9/L for *H. pylori*–negative patients, with no statistically significant difference (p=0.089).

Discussion

The pathogenesis of ITP is not completely clear, and its exact cause has not yet been elucidated. However, the main underlying mechanisms are considered to be an antibody–induced increase in platelet destruction, shortened platelet lifespan and diminished platelet production[9]. Although there is no proven mechanism concerning the pathogenesis, certain theories have been propounded in an attempt to explain the role of *H. pylori* in the development of ITP. These theories are based on the molecular similarity between platelets and *H. pylori* antigens, platelet aggregation, and down–regulation of the reticuloendothelial system[10].

The prevalence of *H. pylori* infection varies between 22% and 85% in patients with chronic ITP[7]. There is not enough evidence to support the routine screening of ITP patients for *H. pylori* or the administration of eradication therapy to patients who are *H. pylori*–negative or patients whose *H. pylori* states are unknown[11]. The predominant view is that appropriate patients with typical ITP can be administered eradication therapy, both due to its low cost and toxicity, and because it can achieve an increase in the platelet count in *H. pylori*–positive patients[7]. Prospective controlled studies conducted

Table II. First-line treatment options and response rates of patients with ITP.

Parameters	*H. pylori*-positive (N=32)	*H. pylori*-negative (N=87)	*p*-value
First-line treatment option, n (%)			0.524
Standard-dose steroid	20 (62.5)	60 (68.9)	
Standard-dose steroid + IVIG	6 (18.8)	16 (18.4)	
High-dose steroid	4 (12.5)	7 (8.1)	
High-dose steroid + IVIG	2 (6.2)	4 (4.6)	
Response rates, n (%)			0.283
Complete response	24 (75)	64 (73.6)	
Partial response	6 (18.8)	17 (19.5)	
No response	2 (6.2)	6 (6.9)	
Final platelet count, $\times 10^9$/L			0.089
Median	214	242	
Range	12-413	7-396	

on this matter by Rostami et al[12] and Suzuki et al[13] showed that platelet count increased in response to *H. pylori* eradication and that this was an appropriate therapeutic option for the patients. Based on this, in our study, we included all patients who did not receive eradication therapy so that the targeted ITP treatment outcome would not be affected. The patients divided into two groups as *H. Pylori*-positive and *H. Pylori*-negative and compared the treatment results.

The primary objective of ITP treatment is to prevent bleeding by raising the platelet count to a constant level. In the absence of bleeding or predisposing comorbid conditions, treatment is rarely required if a platelet count $>50\times10^9$/L is present. It is reported that treatment must only be considered in symptomatic patients with a platelet count lower than 30×10^9/L[14]. All patients in this study had symptoms of active bleeding and/or required treatment according to their platelet count.

The treatment involves medications that increase the platelet count by decreasing the scale of platelet destruction through different mechanisms. Immunosuppressive corticosteroid medications constitute the first-line option among these. In patients who have active bleeding or in whom corticosteroid use is contraindicated, intravenous immunoglobulin or anti–D globulin can be used, either in combination with corticosteroids or as a standalone treatment[15]. First-line treatment options for ITP are similar for all patients, regardless of whether or not a *H. pylori* infection are present[14]. Accordingly, the treatment options received by the two groups in our study were similar and the great majority of the patients had received corticosteroid as the first-line treatment. Where symptoms of bleeding were present and/or a fast increase in platelet count was required, patients received IVIG in combination with standard or high–dose corticosteroids.

The main mechanism underlying the low platelet count seen in *H. pylori*–positive ITP patients is thought to be the destruction of existing platelets by an immune–mediated mechanism rather than a diminution of platelet production. This mechanism was first introduced to the literature by Byrne et al[16] and later confirmed by another study conducted by Teawtrakul et al[17]. In our study, the response rates achieved by the first-line use of immunosuppressive or immunomodulatory medications were similar between *H. pylori*-positive and *H.pylori*-negative patients. Accordingly, the results we obtained in this study corroborate the mechanism described above.

A review of the literature reveals that previous clinical and review studies and have mainly focused on the effects of eradication therapy on the platelet count response in *H. pylori*-positive and *H. pylori*–negative ITP patients[18,19]. The methods and the results of the present retrospective investigation are distinct from other studies. To the best of our knowledge, the present study is unique as its main component is the direct evaluation of response rates to the first-line treatment in *H. pylori*–positive and *H. pylori*-negative ITP patients who did not undergo eradication therapy; and it is valuable in this aspect. The findings of this study may suggest that it is not necessary to routinely screen ITP patients for *H. pylori* before initiating the first-line treatment. However, the difference between the groups with respect to rates of ITP recurrence and response rates to post–recurrence treatment during long–term follow–up have not yet been elucidated. Prospective randomized studies are needed in order to both support our findings and determine the target population that would ob-

tain the maximal benefit from *H. pylori* screening and eradication.

Conclusions

The literature suggests that the platelet count could be increased by standalone eradication therapy without administering conventional ITP treatment. In addition, it can be stated, based on the present study, that response rates to the first-line treatment of ITP without eradication therapy are similar between *H. pylori*-positive and *H. pylori*-negative patients.

Conflict of Interest

The authors of this paper have no conflicts of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Ethics Approval

The study was approved by the Research Ethics Committee of Yuzuncu Yil University, Faculty of Medicine (date/reference number: 24.01.2018/002). All analyses were performed in accordance with the principles of the Declaration of Helsinki.

Informed Consent Statement

Due to the retrospective nature of the study, informed consent was not obtained from the patients.

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Authors' Contributions

Dogan A was responsible for the accuracy and integrity of the study. Dogan A, Ekinci O and Ebinc S analyzed and interpreted the data, prepared the manuscript, performed the statistical analyses, and were responsible for the final editing.

ORCID ID

Ali Dogan: 0000-0003-0207-3505.
Omer Ekinci: 0000-0002-4636-3590.
Senar Ebinc: 0000-0002-0878-6525.

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