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Impact of Eltrombopag Therapy in Different Lines of Treatment on Response in Patients with Immune Thrombocytopenia

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ABSTRACT

Introduction: This study aimed to evaluate the results obtained with the preference of eltrombopag according to the line of treatment in patients diagnosed with ITP.

Methods: This retrospective study included 51 patients who were treated with eltrombopag for chronic ITP at 3 different centers. Diagnosis of ITP was based on the current literature.

Results: Thirty patients (58.8%) received eltrombopag as second-line treatment, 16 patients (31.4%) as third-line, 3 patients (5.9%) as fourth-line treatment, and 2 patients (3.9%) as fifth-line treatment. Twenty-four out of 30 patients (80%) who received eltrombopag as second-line therapy and 12 out of 16 patients who received eltrombopag as third-line therapy demonstrated durable response with no further treatment requirements. Eltrombopag treatment in the second or third line did not affect treatment outcomes (p=0.72).

Conclusion: Eltrombopag in the second or third line of treatment did not have a significant effect on treatment response. The earlier line choice of eltrombopag, duration, and possibility of sustained response should be taken into consideration. The lack of a significant relationship between the line of treatment and response to eltrombopag as a TPO-RA should be considered encouraging in terms of long-term follow-up.

Keywords: Eltrombopag, immune thrombocytopenia, treatment

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts originating from anti-platelet autoantibodies. For the diagnosis of ITP, the elimination of other comorbidities that may cause thrombocytopenia should be ruled out (1). ITP is usually managed with immunosuppressive agents. Corticosteroids represent the first line of choice; prednisone (1 mg/kg/day) with gradual tapering or dexamethasone (40 mg/day) for 4 days are usually preferred glucocorticoid regimens and recommended as the initial choice (2). Several cases of ITP do not maintain sustained remission after the initial therapy and require second-line regimen (3). The choice of second-line treatment options, including rituximab, splenectomy, and thrombopoietin receptor agonists (TPO-RAs), depended on the duration of response to first-line treatment, patient age and request, and accessibility.

Eltrombopag, a member of TPO-RAs, binds to the juxtamembrane domain of the thrombopoietin receptor and induces megakaryocyte proliferation, differentiation, and platelet production through the JAK/STAT, AKT, and MAPK pathways (2,4). Although steroids and intravenous immunoglobulins are effective in obtaining a response in a short time, with rapid effects during the course of ITP; their role in the later phases of the disease is controversial (6). Several studies have demonstrated the effect of eltrombopag in patients with steroid-refractory ITP (2,4).

Although the role of eltrombopag in the second-line treatment of ITP is solid, there are insufficient data regarding response rates with the use of TPO-RAs in later lines. The main aim of our study was to evaluate the results obtained with the preference of eltrombopag according to the line of treatment in patients diagnosed with ITP.

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Methods

In this retrospective study, 51 patients who were treated with eltrombopag for chronic ITP at 3 different centers were included. The diagnosis of ITP was based on the current literature (7). Diagnosis requires isolated thrombocytopenia (<100,000/mm^3) without another known comorbidity or underlying pathologies. Patients aged 18 years and above, diagnosed with ITP for more than 6 months, with a baseline platelet count of 30,000/mm^3, and who relapsed after one or more previous treatments were eligible for TPO-RA use.

Patients' demographic data (age and gender), bleeding score for ITP, laboratory results, such as white blood cell, platelet, neutrophil, and lymphocyte counts, hemoglobin level at the time of splenectomy or beginning of eltrombopag, and dates of diagnosis were recorded. The ITP bleeding score was calculated based on the bleeding scale of the World Health Organization. Patients were classified according to the five-point Likert scale as follows: 0, no bleeding; 1, mild blood loss; 2, gross blood loss; and 3, debilitating blood loss with a score of 4 (8).

Responses were classified as follows: Complete response with a platelet count >100,000/mm^3, partial response with a platelet count between 30,000 and 100,000/mm^3 with at least a 2-fold increase in the initial platelet count, and no response with a platelet count of <30/mm^3.

The minimum dose of eltrombopag that ensured a platelet count of >50,000/mm^3 was used for the patients. The treatment dose was increased by 25 mg in patients with a platelet count of <50,000/mm^3. Eltrombopag dosage was decreased by 25 mg in patients with a platelet count of >150,000/mm^3 and discontinued in patients with a platelet count of >250,000/mm^3. Other treatment options were considered in patients who did not respond to a maximum of 75 mg of therapy.

This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinical Research Ethics Committee (approval number: 18, date: 27.01.2023).

Statistical Analysis

Data were analyzed using the SPSS 24 package. program. The mean and standard deviation, median, minimum, and maximum values of the features, frequency, and percentage values were used to identify categorical variables. Mann-Whitney U test was used to evaluate the effect of initial platelet count on treatment with eltrombopag. Pearson's chi-square test was used to compare categorical variables. Fisher's exact test was preferred for small frequencies. The statistical significance level of the data was given as $p<0.05$.

Results

The patient characteristics are summarized in Table 1. The median age of the patients was 52.3 years (range, 19-84) with 29 women and 22 men. The median number of white blood cells was 9,293/mm^3 (range, 4290-25,480), hemoglobin was 12.6 g/dL (range, 6-16.5) and platelet count was 14,000/mm^3 (range, 0-43,000). Thirty-two patients (62.7%) underwent bone marrow biopsy during diagnosis or follow-up. Among the 17 patients (33.3%) who presented with bleeding. Forty-six patients (90.2%) received methylprednisolone and 5 patients (9.8%) received dexamethasone as first-line treatment.

Thirty patients (58.8%) received eltrombopag as second-line treatment, 16 patients (31.4%) as third-line, 3 patients (5.9%) as fourth-line treatment, and 2 patients (3.9%) as fifth-line treatment.

Twenty-four out of 30 patients (80%) who received eltrombopag as second-line therapy and 12 out of 16 patients who received eltrombopag as third-line therapy demonstrated durable response with no further treatment requirements. Eltrombopag treatment in the second or third line did not affect treatment outcomes ($p=0.72$). There were no significant differences between these two groups in terms of age, gender, platelet count, white blood cell count, and hemoglobin levels (0.5, 0.76, 0.5, 0.76, 0.8) (Table 2).

Treatment responses were obtained in all 3 patients who received eltrombopag in the fourth line and in one of the 2 patients who received it in the fifth line.

Discussion

Among the patients included in our study, 30 (58.8%) were in the second, 16 (31.4%) in the third, 3 (5.9%) in the fourth, and 2 (3.9%) in the fifth line of treatment. Our results revealed that the use of eltrombopag in the second or third line of treatment did not have a significant

Table 1. Baseline characteristics of patients

Sex, n (%)	
Female	29 (56.9)
Male	22 (43.1)
Age, year (median)	52.3 (19-84)
White blood cell count at diagnosis, median (mm^3)	9,293 (4,290-25,480)
Hemoglobin level at diagnosis, median (g/dL)	12.6 (6-16.5)
Platelet count at diagnosis, median (mm^3)	14,000 (0-43,000)
Bone marrow aspiration biopsy, n (%)	
Yes	32 (62.7)
No	19 (37.3)
Bleeding at diagnosis, n (%)	
Yes	17 (33.3)
No	34 (66.7)
1. Line treatment rate, n (%)	
Methylprednisolone	46 (90.2)
Dexamethasone	5 (9.8)
2. Line treatment rate, n (%)	
Eltrombopag	30 (8.8)
Azothiopurine	2 (3.9)
Splenectomy	8 (15.7)
Rituximab	9 (17.6)
Cyclophosphamide	1 (2)
Vincristine	1 (2)
Eltrombobag step, n (%)	
2	30 (58.8)
3	16 (31.4)
4	3 (5.9)
5	2 (3.9)

Tablo 2. Comparison of patients who received eltrombopag between lines 2 and 3

	Eltrombopag in the 2nd step, (n=30)	Eltrombopag in the 3rd step, (n=16)	p-value
Response to treatment, n (%)	24 (80)	12 (75)	0.72
White blood cell count, median (mm^3)	7,525 (4,290-25,480)	9425 (5,900-19,200)	0.76
Age, year (median)	52 (19-84)	49 (27-80)	0.496
Hemoglobin, median (g/dL)	13.2 (6-16.5)	13.3 (7.50-16.30)	0.818
Sex			
Female	17 (56.7)	8 (50)	0,76
Male	13 (43.3)	8 (50)	
Platelet	14,500 (0-43,000)	11,500 (1,000-35,000)	0.496

effect on treatment response. A serious debate exists on ITP and its treatment algorithm, continues and the early use of TPO-Ras, including eltrombopag, is an important area of research.

A study conducted in 2021 compared the effectiveness and toxicity of splenectomy and eltrombopag as second-line treatment options in 38 patients who underwent splenectomy and 47 patients who underwent eltrombopag. Time to response was significantly shorter with splenectomy than with eltrombopag (p=0.001), but no difference was found between the two arms in terms of overall and 2-year response rates (9). In this meta-analysis including a total of 1202 patients with ITP, the effectiveness and safety of second and subsequent lines of treatment were evaluated. Romiplostim was found to be the most suitable treatment option, followed by avatrombopag, eltrombopag, fostamatinib, and rituximab. The early response rate of romiplostim (platelet count ≥50,000/mm^3 at week 2 after initiation of treatment) was superior to avatrombopag, and no significant difference was observed in terms of serious side effects (10). It seems that long-term follow-up, response, and side effects were evaluated in terms of preference for 2nd or other lines of treatment, but there is no sufficient data on the difference in treatment preference between lines of treatment.

Cuker et al. (11) compared patients who received second-line treatment, including eltrombopag, romiplostim, rituximab, splenectomy, and other immunosuppressive agents, within 3 months after the diagnosis with patients who only received first-line treatment. The authors observed that early second-line treatment was used in more severe patients and that corticosteroid use was reduced. In this study, platelet levels improved and bleeding events decreased in all treatment arms; however, the relative platelet increase was lower in those who did not receive early second-line treatment (11). The use of TPO-RAs in patients in the early stages or those with a history of more serious or frequent bleeding is an important area of research and addresses many clinical questions. The findings of our study revealed that the use of eltrombopag in the second or third line of treatment did not have a statistically significant effect on treatment response. It should be taken into consideration that adding eltrombopag into earlier lines of treatment, especially in patients with severe or frequent bleeding events, will help prevent severe bleeding and achieve safe platelet levels. Eltrombopag should be considered an important treatment option in any line of treatment, especially in the presence or history of major bleeding.

Discontinuation of treatment and sustained response after TPO-RA use is reported in 10-30% of patients (12,13). In a study evaluating a total of 260 patients with ITP, 49 patients were examined after discontinuation of eltrombopag, and 26 showed a sustained response without the need for any immunosuppressive agent (14). The median follow-up period was 9 months (range, 6-25 months), the median number of lines of treatment was 4, and 42% of the lines were splenectomized (15). In another study, TPO-RA was discontinued in 20 of 28 patients with complete response; sustained response was achieved in 8 patients (median: 13 months (range, 5-27) (11). Another study examined treatment discontinuation in a total of 31 patients diagnosed with chronic ITP who achieved durable responses with TPO-RA; a sustained response was observed in 9 patients without the need for additional immunosuppressive therapy (15). Of the 9 patients included in the study, 6 had a sustained response after romiplostim and 3 after eltrombopag; all patients were diagnosed with ITP with a median age of 7.8 years, had a median of 4 lines of treatment, and 8 of them were splenectomized (15). In another retrospective study, a total of 53 patients were analyzed, and there was no significant difference in any of the subgroups depending on age, sex, duration of disease, number of prior lines of treatment, splenectomy, or baseline platelet count (16). The fact that the use of eltrombopag in the 2nd or 3rd line of treatment did not have a significant effect on treatment response in our study, when evaluated together with the studies in the literature, may encourage the use of eltrombopag, especially in the early stages. It can also be considered an advantage when considering the sustained response rates.

Study Limitations

There are important limitations in our study. The limited number of patients was the most significant limitation. Therefore, it was not possible to conduct detailed subgroup analyses.

Conclusion

In conclusion, in our study, 30 of patients (58.8%) were in the second, 16 (31.4%) in the third, 3 (5.9%) in the fourth, and 2 (3.9%) in the fifth line of treatment. The use of eltrombopag in the second or third line of treatment did not have a significant effect on treatment response. Early line selection for eltrombopag, duration, and possibility of sustained response should be taken into consideration. The lack of a significant relationship between the line of treatment and response to

eltrombopag as a TPO-RA should be considered encouraging in terms of long-term follow-up.

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinical Research Ethics Committee (approval number: 18, date: 27.01.2023).

Informed Consent: Retrospective study.

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