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Original Article

Does the eltrompobag treatment safe or effective for refractory chronic immune thrombocytopenia patients?

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Abstract: Background: Immune thrombocytopenia (ITP) is a heterogeneous autoimmune disorder characterized by immune-mediated platelet destruction and reduced platelet production. As the pathophysiology of the disease got clear, thrombopoietin receptor (TPO-R) agonists have been preferred in recent years, which seems to be an effective option in the treatment of resistant cases. Eltrombopag, a TPO-R agonist, is a second or third line medical treatment option for adults with chronic ITP. Objective: To determine the efficacy and safety of long-term eltrombopag treatment in treatment-refractory patients with primary ITP was the aim of this study. Materials and Methods: Retrospective data of 34 patients with refractory ITP who were treated with eltrombopag were examined. Efficacy and safety of the eltrombopag treatment was evaluated. Results: The total rate of response was 82%, and the median duration of response defined as the number of the platelets being over 50×10^9/L was 14 (interquartile range: 7-28) days. In two patients, thrombosis was observed with no other additional risk factors due to or related to thrombosis. Conclusion: In spite of the fact that the responses to eltrombopag were satisfactory, patients need to be monitored closely for increasing platelet counts as well as thromboembolic events.

Keywords: Immune thrombocytopenia, thrombopoietin receptor agonist, thrombosis, eltrombopag

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by immune-mediated platelet destruction and reduced platelet production caused by antiplatelet autoantibodies, leading to a marked decrease in platelet count and rarely life-threatening bleeding [1]. In adults, the course of the disease is commonly chronic. The primary goal of treatment is to prevent bleeding by increasing the platelet count to a stable level while managing the few treatment-related toxic effects. Current guidelines suggest that treatment should only be considered in symptomatic patients with platelet counts of less than 30×10^9/L. Treatment is rarely indicated for patients with platelets of $>50\times10^9$/L in the absence of bleeding or predisposing comorbid conditions [1, 2]. First-line treatments for chronic ITP include corticosteroids, intravenous immunoglobulins and anti-D globülin [3]. These drugs increase platelet counts primarily by reducing the extent of platelet destruction by several different mechanisms. In the case of glucocorticosteroid treatment failure, splenectomy is the main second-line therapy and induces a 70%-80% response rate [4]. Different options exist for patients who do not undergo or do not respond to splenectomy including IVIg, IV anti-D, rituximab, danazol, azathioprine, vinca alkaloids, and cyclophosphamide. Recent consensus statements and guidelines recommend TPO-R agonists as second- and third-line treatments [3, 5].

Eltrombopag is the first oral, nonpeptide TPO-R agonist approved for the treatment of chronic ITP in patients with insufficient response to at least one other therapy. Eltrombopag increases platelet production by binding to the transmembrane domain of the TPO-R; it does not compete with endogenous TPO in vitro and it induces proliferation and differentiation of BM progenitor cells in the megakaryocyte lineage [6] In

Table 1. Demographical and clinical characteristics of the patients

Sex (Female/Male)	24/10
Age (years) [median (interquartile range, IQR)]	61 (19-97)
Baseline platelet count $\times 10^9$/L	8000 (3000-27,000)
Final platelet count $\times 10^9$/L	244.8±18.5
Splenectomy N (%)	30 (88.2%)
Number of previous treatments	3 (interquartile range: 3-4)

a phase 3, double-blind, placebo-controlled study of previously treated ITP patients (RAISE), 79% of patients showed an optimal response to eltrombopag treatment compared with placebo treatment [7]. A recently published long-term study of eltrombopag revealed sustained long-term efficacy and safety after 3 years of treatment [8]. In this study, we aimed to assess the efficacy, long-term safety, and tolerability of eltrombopag from two single centers in Turkey.

Materials and methods

This retrospective study was conducted at the Hematology Departments of Dicle University School of Medicine, and Ankara Abdurrahman Yurtaslan Training and Research Hospital in Turkey. A total of 34 patients who received eltrombopag treatment for refractory chronic ITP from these 2 centers in the Turkey were included. All analyses were performed in accordance with the principles of the Declaration of Helsinki. The study was approved by the ethics committee at Ankara Abdurrahman Yurtaslan Training and Research Hospital.

ITP diagnosis was verified according to the International Consensus Report on the Investigation and Management of Primary ITP [9]. Patients were aged 18 years and older and had primary ITP of more than 6 months duration, had baseline platelet counts of lower than 30,000/μL, and had relapsed after two or more previous treatments for their disorder. Date of the first diagnosis of the patients, demographic data, and time to splenectomy, previous treatments and response to treatments, side effects, posttreatment follow-up period, and other such records were retrospectively evaluated. Bleeding was assessed with the World Health Organization bleeding scale (grade 0: no bleeding, grade 1: petechiae, grade 2: mild blood loss, grade 3: gross blood loss, grade 4: debilitating blood loss) [10]. Response rates were defined as follows: complete response when the platelet count was 100×10^9/L, partial response when the platelet count ranged between 30 and 100×10^9/L with at least a 2-fold increase in the initial platelet count, and no response when the platelet count was 30×10^9/L [2].

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate the distribution of data. Data with normal distribution were reported as mean ± standard deviation (SD), while data with non-normal distribution were reported as medians (interquartile ranges, 25%-75%). For comparison of categorical variables, Pearson's chi-square test was used, or in the case of small frequencies, Fisher's exact test was used. Statistical significance was defined as $P<0.05$.

Results

Demographical and clinical characteristics of the patients were presented on **Table 1**. The median age was 61 (IQR 19-97). Twenty four patients (70%) were women. All of them had received glucocorticosteroids at various doses as first-line treatment, and splenectomy was implemented in 30 cases as second-line treatment due to resistance against steroid treatment. Splenectomy was not performed in 4 cases because of incompatibility for surgery due to comorbid disease or the patient's disapproval.

Prior to eltrombopag treatment, bleeding scale scores were evaluated for each patient and previous treatment numbers were revised and recorded. 55.88% of the patients had grade 1, 20.59% had grade 2, 14.1% had grade 0, and 8.82% had grade 3 bleeding score. Median previous treatment number was found to be 3 (interquartile range: 3-4). 44.12% of the patients had previously received 4, 32.35% had received 3, 20.59% had received 5, and 2.94% had received 2 treatments.

Mean platelet count before treatment was 12.5×10^9/L±9.5×10^9/L. Eltrombopag was initiated at 50 mg/day for all patients and the dose was regulated in accordance with their response to treatment. The total rate of response

Table 2. Outcomes of the treatment

Total rate of response, n/%	28 (82%)
Complete response, n/%	20 (59%)
Partial response, n/%	8 (23%)
No response, n/%	6 (18%)
Number of days with of platelet counts above 50,000	14 (7-28)
Duration of eltrombopag treatment, months	12.82±8.21
Post-treatment mean platelet count (n = 16)	248,964

Table 3. Adverse effects and toxicity of treatment

Sinus venous thrombosis, n	1
Deep venous thrombosis, n	1
Headache, n	8
Nausea, n	5
Erythromelalgia, n	1
Liver transaminase elevations, n	4
Muscle/joint aches, n	1
Fatigue, n	1
Grade 3 bone marrow fibrosis, n	1

was 82% and in the cases with response the median period in which the number of platelets reached over 50×10^9/L was determined as 14 (interquartile range: 7-28) days (**Table 2**). Treatment was stopped in 9 cases since no response was obtained 6 patients.

The gender difference effect for the achievement of response to the treatment was evaluated by Pearson chi-square test, and no significantly difference was observed (P = 0.560). The previously having had splenectomy was also found to be no significant in their response to the treatment (P = 0.240). Various different treatment options such as steroids, anti-D globulin, splenectomy, intravenous immunoglobulin, azathioprine, cyclophosphamide, danazol, vincristine, and rituximab prior to the eltrombopag treatment did not have an impact on eltrombopag response (P>0.05 for all).

In the 25 cases in which bone marrow biopsy was done prior to treatment, bone marrow reticulin was evaluated as grade 1 in 1 case, and as grade 0 in 24 cases. During treatment, 15 patients' bone marrow biopsy was repeated. After eltrombopag treatment, bone marrow reticulin was evaluated as grade 1 in 1 case, and grade 3 in 1 case. Eltrombopag treatment of the patients with grade 3 fibrosis was discontinued. Eltrombopag was discontinued in nine patients due to primary resistance (six patients), thrombosis (two patients) and grade 3 fibrosis (one patient). Adverse effects due to treatment are summarized in **Table 3**.

One female patient at the age of 19 was detected to have cerebral venous sinus thrombosis and pregnancy at the same time. She had no other additional risk factors from hereditary thrombophilia of thrombosis. She was receiving 50 mg eltrombopag and had a platelet value 1.200×10^9/L when cerebral venous sinus thrombosis occurred. Eltrombopag treatment was discontinued, and low molecular weight heparin treatment was started. Platelet counts were normal levels during and after pregnancy. Despite taking 3 months of Eltrombopag treatment during pregnancy, she gave birth to a healthy baby.

Deep venous thrombosis occurred in a female patient at the age of 70. She was receiving 50 mg eltrombopag and had a platelet value 1.095×10^9/L. She had no other additional risk factors from hereditary thrombophilia of thrombosis. Eltrombopag treatment was discontinued, and low molecular weight heparin treatment was started. There was no drop in platelet counts during follow-up.

Of the cases with response to treatment, headache in 8 cases, drug-related nausea in 5 cases, muscle/joint aches in 1 case and fatigue in 1 case developed. However, drug use was continued and these adverse effects vanished in a few weeks. Transaminase levels were normal ranges prior to eltrombopag therapy for all patients. Liver transaminase elevations were observed in 4 cases however, toxicity grades were less than grade 2. Eltrombopag treatment was continued in these patients. Grade 3 bone marrow fibrosis was observed in one patient who was suffering from erythromelalgia; thus eltrombopag treatment was discontinued.

Discussion

The current study yielded that eltrombopag treatment is safe and tolerable for treatment-refractory patients with primary ITP.

Total response rate was 80% obtained in the study of Katsutani et al., where 3 years of

eltrombopag data from 19 patients were evaluated, and the rate obtained in the study of Tomiyama et al. including 23 patients with a placebo control was 69.6% [11, 12]. In Turkey 2 different studies showed that total response rate was 87% and 83.9%, respectively [13, 14]. In our study, eltrombopag treatment resulted in platelet counts greater than 50×10^9/L 82% of the patients. Response was sustainable during 92 weeks of follow-up with 25-75 mg/day doses of eltrombopag.

Eltrombopag is associated with an increased risk of thromboembolic events, as reported in previous studies. Thromboembolic events were experienced by 5% of the patients in the EXTEND (Eltrombopag Extended Dosing) study during 3-year of follow-up [8]. Ghanima et al., reported the incidence of thromboembolic events was as 2%-4% during treatment with TPO-R agonists. In the RAISE study ('Eltrombopag for management of chronicimmune thrombocytopenia'), three (2%) patients receiving eltrombopag had thromboembolic events [15]. Thromboembolic events were observed in two (5.8%) patients in our study. Current study showed that those thromboembolic events were related to platelets counts. Two patients suffered from thromsosis and both of them had platelets count upper than 1.000×10^9/L.

Headache and nausea were the common side effects of eltrombopag treatment but it did not cause any interruption in the treatment and disappeared spontaneously over time. Hepatotoxicities were observed in four patients less than grade II and none of the patients had interrupted treatment. Liver enzymes should, even so, be monitored prior to and during treatment with eltrombopag. Cataracts (n = 15, 5%) were the most frequently reported in EXTEND study. Fifteen patients reported cataract; 1 had a trauma-induced cataract, 4 developed new cataracts, and 10 had progression of preexisting cataracts. [8]. In our study we observed cataracts in one patient prior to eltrombopag treatment which was prior use of corticosteroids long term. During eltrombopag treatment progression of cataract was not observed. The possibility of a relationship between eltrombopag and cataracts has not been completely excluded and is still being monitored in clinical trials. Regular eye examinations should be advised for high-risk patients or patients with existing cataract [8, 11].

Eltrombopag treatment may increase the risk of developing or progressing reticulin or collagen in bone marrow due to chronic stimulation of megakaryocytes [8]. There has been concern about treatment of chronic ITP patients with TPO-R agonists [17]. In this study, before eltrombopag treatment grade 1 fibrosis was observed in bone marrow biopsy in one patient and during eltrombopag treatment she suffered from erythromelalgia, then bone marrow biopsy was repeated. Grade III fibrosis was observed in bone marrow biopsy posttreatment 20^{th} month and eltrombopag treatment was discontinued. It is unclear if the risk of bone marrow fibrosis is due to TPO-R agonist or the underlying disease. We suggest that for patients on eltrombopag, peripheral blood smears should be examined for morphological abnormalities and if clinical abnormalities develop or deteriorate, a bone marrow biopsy should be performed.

In conclusion, eltrombopag is effective and well tolerated as a second- or third-line treatment option in patients who are intolerant or refractory to second -and/or third-line treatments. Eltrombopag is well tolerated in chronic ITP patients. Although the responses to eltrombopag were satisfactory, patients need to be monitored closely for increasing platelet counts as well as thromboembolic events.

Disclosure of conflict of interest

None.

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