Original Article

Evaluation of Patients with Chronic Immune Thrombocytopenic Purpura Treated with Eltrombopag: A Single Center Experience

Eltrombopag Tedavisi Alan Kronik İmmün Trombositopenik Purpura Tanılı Hastaların Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Introduction: The goal of treatment in chronic immune thrombocytopenia is to keep the platelet count within a safe range that can prevent bleeding. Eltrombopag is an oral thrombopoietin receptor agonist for the treatment of thrombocytopenia. We evaluated the demographic characteristics, eltrombopag treatment response and side-effect profile of a total of 79 patients using eltrombopag with follow-up at our center. By comparing our findings with the literature data, we aimed to reveal the differences in response rates and side-effect profiles.

Materials and methods: A total of 79 patients who were diagnosed with chronic immune thrombocytopenia and used eltrombopag, who applied to the hematology outpatient clinic of our center between January 1, 2010 and May 1, 2021, were evaluated in a randomized retrospective manner. Demographic characteristics of the patients, eltrombopag treatment response, and side-effect profile were recorded. Pearson Chi-square test was used to analyze categorical data.

Results: In our study, the data of 79 patients who received eltrombopag treatment were analyzed retrospectively (45 females-34 males, mean age 49±19.1 years). When the basal platelet count of the patients was evaluated before the treatment, the mean value was calculated as 17,000/mm^3. When all platelet values after eltrombopag treatment were examined, the mean maximum platelet value was 127,000/mm^3, and the mean time to reach the maximum platelet value was 30 days. Complete remission was achieved in 46 (58%) patients, partial remission was achieved in 14 (17%) patients, and 19 (25%) didn't respond. Sixteen (20%) patients had a prolonged response

Discussion: While basal platelet count and treatment responses for eltrombopag treatment were similar to those in the literature, prolonged response rates were higher in our study. Although the rate of elevation in liver enzyme follow-ups in our study was higher than the data in the literature, the rates of having to discontinue the drug for this reason were similar.

Keywords: Eltrombopag, chronic immune thrombocytopenic purpura, remission, prolonged response

ÖZET

Giriş: Kronik immün trombositopenide tedavi hedefi trombosit sayısını kanamayı önleyebilecek güvenli bir aralıkta tutmaktır. Eltrombopag, trombositopeni tedavisinde oral bir trombopoietin reseptör agonistidir. Merkezimizde takipli eltrombopag kullanan toplam 79 hastanın demografik özelliklerini, eltrombopag tedavi yanıtını ve yan etki profilini değerlendirdik. Bulgularımızı literatür verileri ile kıyaslayarak özellikle yanıt oranlarındaki ve yan etki profilindeki farklılıkları ortaya koymayı amaçladık.

Gereç ve yöntemler: Çalışmamıza 1 Ocak 2010–1 Mayıs 2021 tarihleri arasında merkezimizin hematoloji polikliniğine başvuran kronik immun trombositopeni tanısı konulan ve eltrombopag kullanan toplam 79 hasta randomize olacak şekilde retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, eltrombopag tedavi yanıtı, yan etki profili kaydedildi. Kategorik verilerin incelenmesinde Pearson Ki-kare testi kullanılmıştır.

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Bulgular: Çalışmamızda eltrombopag tedavisi alan 79 hastanın verileri retrospektif olarak incelendi (45 kadın-34 erkek, yaş ortalaması 49±19,1 yıl). Hastaların tedavi öncesi bazal trombosit sayısı değerlendirildiğinde ortalama değeri 17,000/mm^3 olarak hesaplandı. Eltrombopag tedavisinden sonraki tüm trombosit değerleri incelendiğinde maksimum trombosit değeri ortalaması 127,000/mm^3, maksimum trombosit değerine ulaşılan ortalama süre ise 30 gün şeklindeydi. Hastaların 46'sında (%58) komplet remisyon, 14'ünde (%17) parsiyel remisyon sağlanırken 19'unda (%25) yanıt alınamadığı izlendi. Hastaların 16'sı (%20) uzamış cevaba sahipti.
Tartışma: Eltrombopag tedavi kararı verilen bazal trombosit sayısı ve tedavi yanıtları literatür ile benzerken, uzamış cevap oranlarının bizim çalışmamızda daha fazla olduğu görüldü. Çalışmamızdaki karaciğer enzim takiplerindeki yükselme oranı literatürdeki verilerden daha yüksek bulunmasına rağmen, bu sebepten ilacın kesilmek zorunda kalınmasının oranları benzerdir.

Anahtar kelimeler: Eltrombopag, kronik immün trombositopenik purpura, remisyon, uzamış cevap

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease in which antiplatelet antibodies accelerate platelet destruction. Most ITP patients are asymptomatic if their platelet count is greater than 50,000/mm^3. However, persistent low platelet count (<20,000 mm^3) is associated with an increased risk of serious bleeding, such as intracranial hemorrhage [1].

The main goal in the management of chronic ITP is to achieve a safe platelet count that can prevent major bleeding in the patient, rather than to normalize the platelet count, thereby reducing treatment-related toxicity as much as possible [2].

Guidelines in the literature recommend corticosteroids as first-line therapy and splenectomy as second-line therapy in ITP. Different options are available for patients who do not or do not respond to splenectomy, such as IVIG (intravenous immunoglobulin), IV (intravenous) anti-D, rituximab, danazol, azathioprine, vinca alkaloids, and cyclophosphamide [3-6].

Eltrombopag is an oral, small molecule, non-peptide thrombopoietin receptor agonist that interacts with the transmembrane domain of the thrombopoietin receptor. The drug interacts with the transmembrane domain of the receptor, initiating thrombopoietin-receptor signaling, thereby inducing proliferation and differentiation of cells in the megakaryocytic lineage. Recent consensus statements and guidelines recommend thrombopoietin-receptor (TPO-R) agonists as second- and third-line therapies [7-11]. Since it does not have as old a history as other drugs used in the treatment of ITP, many international studies are carried out to illuminate the clinical reflections of the drug.

Although headache is the most commonly reported side effect with the use of eltrombopag in ITP, more serious side effects such as increased liver enzymes, cataract development and thrombosis can occur. Such side effects can sometimes lead to discontinuation of treatment [8,9].

In this study, we evaluated the demographic characteristics, eltrombopag treatment response and side effect profile of 79 patients diagnosed with chronic immune thrombocytopenia and using eltrombopag, and aimed to reveal the differences in response rates and side effect profile.

Material and Methods

A total of 79 patients who were diagnosed with chronic immune thrombocytopenia and used eltrombopag, who applied to the Hematology Polyclinic of Eskişehir Osmangazi University Medical Faculty Hospital between January 1, 2010 and May 1, 2021 were included in our study. Demographic characteristics of the patients, eltrombopag treatment response and side effect profile were recorded. In platelet fol-

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Table-1: Demographic Characteristics of the Patients

	n: 79(%)
Median age	49±19,1 years
Age at which the drug was started	53±17,2 years
Gender	
Female	45 (57%)
Male	34 (43%)
Etiology	
Idiopathic	58 (73%)
Secondary	21 (27%)
Splenectomy performed	26 (33%)
Prior treatments	
Steroid	79 (100%)
Intravenous immunoglobulin	69 (87%)
Danazol	23 (29%)
Rituximab	7 (8%)
Azathioprine	2 (2,5%)

low-up after use of eltrombopag, those with the highest platelet count above 100,000/mm^3 at any time were considered complete remission, those between 30,000/mm^3 and 100,000/mm^3 were considered partial remission, and those below 30,000/mm^3 were considered non-responders [8-12]. A prolonged response was defined as platelet values ≥50,000/mm^3 for 12 weeks or longer without the need for any treatment after discontinuation of eltrombopag therapy [12]. Patients with partial or complete response to eltrombopag treatment but unresponsive (<30,000/mm^3) during follow-up were considered eltrombopag resistant [12]. Follow-up and overall survival of the patients were recorded.

E25403353-050.99-214165 approval was obtained from the Eskişehir Osmangazi University Non-Interventional Ethics Committee for the study. All procedures performed comply with the ethical standards of the institution and/or the research committee and the 1964 Declaration of Helsinki and subsequent national amendments or comparable ethical standards.

Statistical Analysis: The obtained data were analyzed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA) program. Kolmogorov-Smirnov test was used to evaluate the distribution of data. The distribution of normal data was reported as mean ± standard deviation (SD), non-normally distributed and non-parametric data were reported as the median (median).The Mann-Whitney U test was used for the comparison of two groups for data not normally distributed. Pearson Chi-square test was used to analyze categorical data. In the statistical evaluation, $p<0.05$ was considered significant.

Results

The follow-up period of the patients who were started on eltrombopag ranged from 15 days to 10 years, and the median follow-up period was determined as 18 months. The duration of use of eltrombopag varied between 8 days and 3285 days, with a median of 90 days. Demographic characteristics of 79 patients included in the study are shown in Table 1.

When the etiology of the patients diagnosed with ITP given eltrombopag was examined, it was seen that 58 patients were idiopathic and 21 patients had secondary ITP. Of the patients with secondary ITP, 13 were secondary to hematological malignancy, four were secondary to autoimmune diseases, two were secondary to solid cancer, and two were secondary to drug/vaccine. Prior to the use of eltrombopag, all patients had received steroid therapy. The previous treatments received by the patients are shown in Table 1.

When the basal platelet count of the patients who were started on eltrombopag treatment was evaluated, the median value was calculated as 17,000/mm^3 (2,000/mm^3- 57,000/mm^3). It was

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Table-2: Response, prolonged response, and resistance to Eltrombopag therapy

	n: 79(%)
Response (≥50,000/mm^3)	54 (68%)
Complete remission (≥100,000/mm^3)	46 (58%)
Partial remission (30,000/mm^3-100,000/mm^3)	14 (17%)
Unresponsive (<30,000/mm^3)	19 (25%)
Prolonged response[1]	16 (20%)
Resistance[2]	8 (10%)

[1]platelet values ≥50000/mm^3 for 12 weeks or longer on any mild side
[2]partial or complete response but no response (<30000/mm^3) at follow-up

Table-3: Side effect profile

	n: 79(%)
Weakness	8 (10%)
Headache	11 (14%)
Nause	3 (4%)
Liver enzyme elevation	13 (16%)
Major bleeding (gastrointestinal)	2 (2,5%)
Minor bleeding (nose, gums, etc.)	7 (9%)
Thromboembolic event	3 (4%)
Cataract	0 (0%)

observed that 32 (40%) of the patients had a thrombocyte value <15,000/mm^3, 47 (60%) had ≥15,000/mm^3 at treatment baseline. When all platelet values after eltrombopag treatment were examined, the median maximum platelet value was 127,000/mm^3 (3,000/mm^3-913,000/mm^3), and the median time to reach the maximum platelet value was 30 days (1 day-495 days).

In response, it was observed that 60 (75%) patients were responsive to this treatment when the platelet count was 30,000/mm^3 and above at any time, and 54 (68%) patients when the platelet count was 50,000/mm^3 and above. The median day on the first day that patients exceeded 30,000/mm^3 after treatment was day 8 (1 day-45 days), while the median day on the first day when patients exceeded 50,000/mm^3 was day 11 (1 day-58 days).

The response status of the patients to eltrombopag treatment is shown in Table 2. Sixteen (20%) of the patients had a prolonged response and no additional drug requirement developed during their follow-up. Most of the patients with prolonged response are still followed up; The median prolonged response time was found to be 16 months (3.5 months - 64 months).

Eight patients (10%) developed resistance during follow-up. The median time to resistance development was 104 days (23 days -1150 days).

There was no statistically significant difference between the responses of the patients receiving eltrombopag treatment to the treatment, gender and age (p:0.109, p:0.393). Similarly, there was no statistically significant difference between treatment response and initial platelet counts, etiology of ITP, and which line of treatment eltrombopagin was given (p:0.223, p:0.192, p:0.161).

The side effects of patients after eltrombopag are shown in Table 3. Two of the thrombo-embolic events were deep vein thrombosis and one was sinus vein thrombosis. Sixteen (20%) of the patients died during their follow-

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up. When the causes of death were examined, it was observed that 9 of them died due to the underlying malignant disease, and three of them died from sepsis. The cause of death of six patients was unknown. Since resistance developed in four of these six patients, it was observed that eltrombopag treatment was discontinued during the follow-up and alternative treatments were started.

Discussion

While the eltrombopag treatment response in our study was 68% similar to the literature, it was observed that the prolonged response rate was 20% higher than the data in the literature. It was observed that only 2.5% of our patients discontinued treatment due to side effects. Although the rate of elevation in liver enzyme follow-ups in our study was higher than the data in the literature, the rates of having to discontinue the drug for this reason were similar.

The median age of patients initiated on eltrombopag was 50 years in the EXTEND study [10], 47 years in the RAISE study [8], Bussel JB. et al. found it to be 47 years [9]. The mean age of onset of eltrombopag in our study was calculated as 53±17.2 years.

The basal platelet value before eltrombopag treatment is lower than 15,000/mm^3 in the literature, which is similar to our study. Percentage of patients with baseline platelet count less than 15,000/mm^3 43% in EXTEND [10], 50% in RAISE [8], Bussel JB. et al. [9], it was found to be 50% in their study, and it was found to be 40% in our study.

In the studies conducted by Cheng et al. in 2011, it was observed that 79% (n=106) of the patients given eltrombopag responded to the treatment [8]. Again, in the experience of 40 patients with eltrombopag from eight different centers in the Aegean Region in our country, the overall response rate was reported to be 87% [13]. Similarly, in our study, a response was observed in 68% of our patients, increasing the platelet count to over 50,000/mm^3.

Saleh MN. et al. In the EXTEND study conducted by [10] with 299 patients, the rate of patients with prolonged response was found to be 4%. In our study, the rate of patients with prolonged response was found to be 20%. It was thought that the existing differences may be due to the fact that the response and effect are affected by many factors such as genetic structure, ethnicity, environmental effects, and the relatively small number of participants in our study.

In our country, the response rate was reported as 77% in the experience of 31 patients with eltrombopag, whose data were scanned in the Ankara Oncology Training and Research Hospital in 2021 [14]. In the same study, the basal platelet count before treatment was determined as 11,000/mm^3, and the median on the first day when it exceeded 50,000/mm^3 was determined as the 17th day [14]. Similarly, in our study, it was observed that 68% of the patients were responsive to treatment. In our study, similar to Ankara data, basal platelet count exceeded 17,000/mm^3 and 50,000/mm^3 and the median of the first day was 11 days.

Saleh MN. et al. Thrombosis developed during treatment in 5% of patients, and treatment was terminated in 2% of patients due to elevated liver enzymes [10]. Similarly, thromboembolic events developed in 4% of patients in our study. Dose reduction was performed in 16% of patients due to liver enzyme elevation. However, only 2.5% of the patients had to discontinue the treatment because the liver enzyme elevation persisted despite the low dose. This situation contributes to the literature in showing that the continuation of the drug is increased with close follow-up and appropriate dose reduction in case of liver enzyme elevation. As a result; Eltrombopag is an effective option in increasing platelet values and reducing

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bleeding symptoms in patients with chronic ITP. It has been well tolerated in the short and long term to date, and long-term efficacy and safety studies are still ongoing.

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