RESEARCH ARTICLE

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Could Antinuclear Antibody Positivity Be a Factor Affecting Treatment Response in Immune Thrombocytopenia Patients on Eltrombopag?

Anti-Nükleer Antikor Pozitifliği Eltrombopag Kullanan İmmün Trombositopeni Hastalarında Tedavi Yanıtını Etkileyen Bir Faktör Olabilir mi?

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Abstract

Objective: Eltrombopag remains a prominent option in the treatment of steroid-dependent or steroid-refractory immune thrombocytopenia (ITP) patients. Unfortunately, not all patients respond to eltrombopag. Antinuclear antibody (ANA) positivity can be seen at rates of up to 30% in ITP patients. Despite being widely used, more markers to predict the response to eltrombopag are still needed. In the present study, we aimed to show the association between ANA positivity and eltrombopag response in ITP patients.

Materials and Methods: Patients who were diagnosed with ITP in the Trakya University Faculty of Medicine's Department of Hematology and who underwent eltrombopag treatment due to their resistance to steroids and other treatments were included in our study. ANA measurement was performed by indirect fluorescent antibody method and titers of 1:160 and above were considered positive. ANA measurements were made before starting eltrombopag.

Results: Forty-five patients were included in our study, 33 being women and 12 men. The mean age of the patients was 45.73 years. There were 14 patients with ANA positivity and 31 patients were found to be ANA-negative. Response rates were higher in ANA-negative patients compared to ANA-positive patients in the 1st and 6th months of eltrombopag treatment ($p<0.05$).

Conclusion: ANA positivity in ITP may indicate unresponsiveness to eltrombopag treatment, a finding that should be further supported by prospective studies involving more patients.

Keywords: Antinuclear antibodies, Eltrombopag, Immune thrombocytopenia

Öz

Amaç: Eltrombopag, steroide bağımlı veya steroide dirençli immün trombositopeni (İTP) hastalarının tedavisinde önemli bir seçenek olmaya devam etmektedir. Ne yazık ki, bir grup hastada eltrombopag ile istenen yanıt oranları elde edilmemektedir. Antinükleer antikor (ANA) pozitifliği İTP hastalarında %30'a kadar görülebilmektedir. Yaygın olarak kullanılmasına rağmen, eltrombopag yanıtını gösteren belirteçler net değildir.Bu çalışmada İTP hastalarında ANA pozitifliği ile eltrombopag yanıtı arasındaki ilişkiyi göstermeyi amaçladık.

Gereç ve Yöntemler: Trakya Üniversitesi Tıp Fakültesi Hematoloji Bölümü'nde İTP tanısı alan ve steroid ve diğer tedavilere dirençli olmaları nedeniyle eltrombopag tedavisi alan hastalar çalışmamıza dahil edildi. ANA ölçümü eltrombopag tedavisi öncesinde gerçekleştirildi ve indirekt floresan antikor ile yapıldı. ANA için 1:160 ve üzeri titreler pozitif kabul edildi.

Bulgular: Çalışmamıza 45 hasta dahil edildi. Hastaların 33'ü kadın, 12'si erkekti. Hastaların yaş ortalaması 45,73 idi. ANA pozitif olan 14 ve negatif olan 31 hasta vardı. Eltrombopag tedavisinin birinci ve altıncı aylarında ANA negatif hastalarda ANA pozitif hastalara göre yanıt oranları daha yüksek olarak saptandı ($p<0,05$).

Sonuç: İTP'de ANA pozitifliğinin eltrombopag tedavisine yanıtsızlığa işaret edebileceğini ve bu durumun daha fazla hastayı içeren prospektif çalışmalarla desteklenmesi gerektiğini düşünmekteyiz.

Anahtar Sözcükler: Anti-nükleer antikorlar, Eltrombopag, İmmün trombositopeni

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Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by a low platelet count caused by increased destruction of thrombocytes due to platelet autoantibodies and impaired platelet production [1,2]. The diagnosis of ITP is made by exclusion. Primary ITP occurs without an underlying disease, while secondary ITP is defined as ITP occurring with an underlying disease or facilitating factor [3]. The antibodies that target proteins within the nucleus of a cell are called antinuclear antibodies (ANAs). ANA positivity can be detected in about 5%-10% of healthy individuals [4,5], while ANA positivity was reported at rates between 15% and 39% in studies conducted with ITP patients [6,7,8]. It has also been reported that ANA positivity in ITP patients is associated with a more chronic course and the risk of developing more autoimmune diseases [9]. Accordingly, testing for ANA was suggested as being of potential utility according to an international consensus report on the investigation and management of primary ITP [10]. The first-line treatment of ITP consists of corticosteroids and intravenous immunoglobulin. For patients who are corticosteroid-dependent or who do not have a response to corticosteroids, the recommended treatment options are thrombopoietin receptor agonists (TPO-RAs), splenectomy, and rituximab [11]. Eltrombopag and romiplostim are the currently licensed TPO-RAs for ITP. Eltrombopag is an orally available nonpeptide TPO-RA and is accessible in Turkey.

Approximately 10% to 30% of patients receiving eltrombopag have a permanent improvement in platelet values and drug administration can be discontinued [12]. However, some patients may be unresponsive to TPO-RAs [13]. In some cases, the addition of small doses of steroids to TPO-RAs may be required to maintain thrombocyte levels [14]. The variety of responses to TPO-RAs indicates the need for factors to be identified for prediction. Regarding such factors, ANA was suggested as a test of potential utility according to an international consensus report; however, the real utility of positive ANA test results in ITP patients has yet to be determined. The results of studies on the effect of ANA positivity on treatment in ITP are conflicting [15,16,17]. Because ANAs are antibodies demonstrating a predisposition to autoimmunity, ANA positivity may affect the response rates in patients with ITP who receive eltrombopag treatment. In the present study, we aim to investigate the association between ANA positivity and eltrombopag response in patients with ITP.

Materials and Methods

Patients who were diagnosed with ITP in the Trakya University Faculty of Medicine's Hematology Department and who underwent eltrombopag treatment due to their resistance to steroids and other treatments were included in this study. The starting dose in eltrombopag treatment is 50 mg once a day; for patients who do not respond with 50 mg, the dose is increased to 75 mg daily. If the platelet count exceeds $250,000x10^9$/L, treatment is stopped. For patients whose treatment is discontinued because the platelet count exceeds 250,000, the treatment is restarted with a daily dose of 25 mg when the thrombocyte count falls below 100,000. ANA measurements were made by indirect fluorescent antibody method and titers of 1:160 and above were considered positive. All other investigations performed for patients with ITP were recorded from their hospital files. Hepatitis B, hepatitis C, and HIV serology of the patients were evaluated. Serum immunoglobulin G levels and direct antiglobulin tests were also reviewed. ANA-positive patients were also evaluated for other clinical and laboratory findings of systemic lupus erythematosus [18]. Response criteria were as follows: (1) complete response (CR): platelet count of $\geq 100x10^9$/L and no bleeding; (2) response (R): platelet count of $\geq 30x10^9$/L and no bleeding; (3) no response: platelet count of $<30x10^9$/L or bleeding. Recurrence was defined as a decrease in platelet count to $<30x10^9$/L and/or bleeding in responders [3]. Ethical approval to conduct the study was obtained from the institutional review board and the study was carried out in accordance with the 1964 Declaration of Helsinki and its later amendments. Patients who could not achieve a response with eltrombopag were administered rituximab at 375 mg/m^2 for 4 weeks as an additional treatment for ITP.

Statistical Analysis

For statistical analysis, SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used and a two-sided p-value below or equal to 0.05 was considered statistically significant. Descriptive statistics were given as number, percentage, and mean ± standard deviation. Chi-square and Fisher exact tests were used in the analysis of categorical variables. Chi-square contingency analysis was also performed due to the small sample size. Continuous variables were compared using the Mann-Whitney U test.

Results

A total of 45 patients were included in our study; 33 were female and 12 were male. The mean age of the patients was 45.73 years. There were 14 patients with ANA positivity and 31 patients were found to be ANA-negative. Demographic and clinical findings are given in Table 1. Of the 14 ANA-positive patients, 13 were female and 1 was male. Of the 31 ANA-negative patients, 20 were female and 11 were male. Detailed demographic data of the patients according to ANA positivity are given in Table 2. Response rates of the patients were evaluated according to their thrombocyte count during the 1st month, 3rd month, and 6th month of treatment. Response assessments are presented in Table 3. One patient developed pulmonary emboli and grade 3 hyperbilirubinemia occurred in another patient; eltrombopag

Table 1. Demographic and clinical data of the patients.

Parameter	Number (%)
Gender Female Male	 33 (73%) 12 (27%)
Age, mean (minimum-maximum)	45.73±18.86 (18-85)
ANA-positive ANA-negative	14 (31%) 31 (69%)
Mean platelet count before eltrombopag treatment, x10^9/L	13.9±7.2
Number of prior line of therapies One Two	 39 (87%) 6 (13%)
Splenectomy before eltrombopag	3 (6.6%)
Concomitant ITP treatment with eltrombopag	4 (8.8%)
Rituximab treatment before eltrombopag	3 (6.6%)

ANA: Antinuclear antibody; ITP: immune thrombocytopenia.

treatment was discontinued in both cases. Therefore, at 6 months, the analysis was performed with 43 patients. Response rates were higher in ANA-negative patients than ANA-positive patients in the 1st and 6th months of eltrombopag treatment ($p<0.05$).

Discussion

Various autoimmune antibodies have been shown to be more positive in ITP patients than in healthy individuals. Positive ANA tests in ITP patients were associated with poor response to steroids and a more chronic disease outcome [7,9,15]. Similar to this finding, in a retrospective analysis that included 1330 cases of chronic childhood ITP, ANA positivity was associated with more persistent and chronic disease [19]. In another recent study, ANA positivity was associated with a higher risk for thrombosis in ITP patients [16]. In that analysis, positive ANA test results were obtained in 65% of the study population. The cut-off for positive ANA titer was taken as 1:40 or above.

Table 2. Detailed demographic data and thrombocyte counts of the patients according to ANA positivity.

	ANA-positive patients n: 14	ANA-negative patients n: 31	p
Gender Female Male	 13 1	 20 11	0.070
Age	46	45.6	0.950
Baseline thrombocyte count, x10^9/L	13.4 (4- 14- 26)	14.2 (4- 14- 29)	0.724
Thrombocyte count at 1st month, x10^9/L	77.2 (9- 53- 288)	159.8 (12- 127- 646)	0.035
Thrombocyte count at 3rd month, x10^9/L	144.1 (15- 107- 495)	144.4 (3- 110- 523)	0.783
Thrombocyte count at 6th month, x10^9/L	104.1 (12- 109- 295)	156.3 (31- 143- 577)	0.133
History of splenectomy before eltrombopag	2 (14.2%)	1 (3.2%)	0.368
Additional rituximab treatment with eltrombopag	3 (21.4%)	1 (3.2%)	0.459
Rituximab treatment before eltrombopag	2 (14.2%)	1 (3.2%)	0.368
Duration of ITP, months, median (minimum-maximum)	43 (11-211)	30 (6-201)	0.203

ANA: Antinuclear antibody; ITP: immune thrombocytopenia.

Table 3. Response rates for ANA-positive and ANA-negative patients.

	ANA-positive n: 14	ANA-negative n: 31	p
1st month Complete response Response No response	 2 (14.3%) 9 (64.3%) 3 (21.4%)	 17 (54.8%) 9 (29.0%) 5 (16.2%)	**0.034**
3rd month Complete response Response No response	 7 (50%) 5 (35.7%) 2 (14.3%)	 21 (67.7%) 6 (19.3%) 4 (13.0%)	0.640
6th month Complete response Response No response	 7 (53.8%) 4 (30.8%) 2 (15.4%)	 22 (73.3%) 7 (23.3%) 1 (3.3%)	**0.019**

It was also observed that when ANA positivity was taken as a titer of 1:80, the rate of ANA positivity decreased to 44%. In another retrospective analysis, ANA positivity was found in 24.4% of the patients and ANA-positive patients had a poorer response to initial steroid therapy compared to ANA-negative patients [14]. In our analysis, ANA positivity was found in 31% of cases, similar to the data in the literature. A recent prospective study included 278 primary ITP patients, and in that registry, neither complete response rates nor thrombosis during follow-up periods were different for ANA-positive and ANA-negative patients [17]. In another retrospective analysis, the authors aimed to show differences in responses in primary ITP patients receiving rituximab therapy. ANA-positive patients tended to respond better compared to ANA-negative patients in the initial evaluation in the 1st month [20]. ANA-positive patients constituted 34.1% of the study population. However, ANA-positive patients' response rates waned with time in the follow-up period and the response rates of ANA-negative patients in the 6th, 12th, and 24th months were found to be better [20]. In our analysis, ANA-positive patients' response rates were lower in the 1st month, similar in the 3rd month, and lower in the 6th month compared to ANA-negative patients. Although the follow-up period in our study was shorter than that of the previously mentioned study [17], we also showed that response rates decreased over time in ANA-positive patients who received eltrombopag treatment. The efficacy of eltrombopag treatment in chronic ITP was also demonstrated in studies using real-world data [21,22,23]. Nevertheless, some patients do not respond well to eltrombopag therapy. Factors and indicators that can predict response rates should be identified. Our study population included steroid-resistant or steroid-dependent patients, which could be another factor for the low response rates seen in ANA-positive patients. The two main limitations of our study are the short follow-up period and small sample size.

Conclusion

ANA positivity in ITP may indicate unresponsiveness to eltrombopag treatment, and this should be supported by prospective studies involving more patients.

Ethics

Ethics Committee Approval: Ethical approval to conduct the study was obtained from the institutional review board and the study was carried out in accordance with the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: Written informed consent was obtained from all patients.

Authorship Contributions

Concept: M.B.; Design: M.B., E.Ü.; Data Collection or Processing: V.B., M.B.; Analysis or Interpretation: H.O.K., A.M.D.; Literature Search: M.B.; V.B.; Writing: M.B., E.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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