RESEARCH ARTICLE

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Quadruple Therapy in Patients with Immune Thrombocytopenia

ABSTRACT

Objective: In the treatment of immune thrombocytopenia dexamethasone, rituximab, and cyclosporine combination therapies provided promising results in recent years. This study aimed to investigate the responses of patients with quadruple therapy which created by combining combinational therapies given in immune thrombocytopenia with eltrombopag.

Methods: Four patients diagnosed with immune thrombocytopenia who received steroid in the first-line treatment and eltrombopag in the second-line treatment without achieving complete remission/partial remission were retrospectively evaluated in terms of the treatment they received and response rates.

Results: received and response rates.

Results:Patients with relapsed/refractory immune thrombocytopenia were treated by oral dexamethasone, oral cyclosporine and intravenous low-dose rituximab in addition to eltrombopag therapy. Eltrombopag treatment was continued at a dose of 50mg/day. No loading dose was given for cyclosporine, weekly blood cyclosporine level was monitored for toxicity and the treatment was titrated to a target dose of 200 to 400 µg/L. No toxicity-induced death, serious treatment-related adverse events, or non-adherence to treatment were observed. The 6-month response rate was 75% and the treatment was well tolerated. Two patients were still followed up by us with a complete response, while one our patient underwent splenectomy because of relapse after 6 months and is still being followed up with eltrombopag therapy. In one our patient, which was unresponsive, romiplastim treatment was applied but there was no response to this treatment either. The patient was referred to a clinical study.

Conclusions: Our study showing that a combination of quadruple therapy can be a treatment option in patients with treatment-resistant immune thrombocytopenia is promising.

Keywords: Immune Thrombocytopenia, Eltrombopag, Quadruple Therapy.

İmmun Trombositopenili Hastalarda Dörtlü Tedavi

ÖZET

Amaç: İmmün trombositopeni tedavisinde son yıllarda deksametazon, rituksimab ve siklosporin kombinasyon tedavileri umut verici sonuçlar vermiştir. Bu çalışmada, immün trombositopenide verilen kombinasyon tedavilerinin eltrombopag ile birleştirilmesiyle oluşturulan dörtlü tedavinin hastalardaki yanıtlarının araştırılması amaçlanmıştır.

Gereç ve Yöntem: İmmun trombositopeni tanısı almış birinci basamak tedavide steroid, ikinci basamak tedavide eltrombopag alan, tam ya da kısmı remisyon sağlanamayan dört hasta retrospektif olarak aldıkları tedavi ve yanıt oranları açısından değerlendirildi.

Bulgular: Relaps /refrakter immün trombositopenisi olan hastalar, eltrombopag tedavisine ek olarak oral deksametazon, oral siklosporin ve intravenöz düşük doz rituksimab ile tedavi edildi. Eltrombopag tedavisine 50 mg/gün dozunda devam edildi. Siklosporin için yükleme dozu verilmedi, haftalık kan siklosporin düzeyi toksisite açısından izlendi ve tedavi 200 ile 400 µg/L'lik bir hedef doza titre edildi. Toksisite kaynaklı ölüm, tedaviye bağlı ciddi advers olaylar veya tedaviye uyumsuzluk gözlenmedi. 6 aylık yanıt oranı %75 idi ve tedavi iyi tolere edildi. Hastalarımızdan iki tanesi halen tam yanıtlı olarak tarafımızca takipli iken bir hastamızda 6.aydan sonra relaps olması nedeniyle splenektomi yapılmış olup halen eltrombopag tedavi ile takiplidir. Yanıtsız olan daha önce splenektomili olan hastamıza ise romiplastim tedavisi uygulandı ancak bu tedaviye de yanıt alınamadı. Hasta klinik çalışmaya dahil edildi.

Sonuç: Tedaviye dirençli immün trombositopenili hastalarda dörtlü tedavi kombinasyonunun bir tedavi seçeneği olabileceğini gösteren çalışmamız umut vaad etmektedir.

Anahtar Kelimeler: İmmun Trombositopeni, Eltrombopag, Dörtlü Tedavi.

INTRODUCTION

Immune thrombocytopenia (ITP) is a disease with an increased risk of hemorrhage developing on an autoimmune basis, which is caused by increased platelet destruction or decreased platelet production, affecting both children and adults (1-3). While it results in complete remission in 80% of children within 3-6 months, it usually becomes chronic in adults (4). The most common symptoms are petechiae and hemorrhage (5). While platelet count is mostly used to evaluate disease status and response to treatment; hemorrhage is the most important factor in clinical prognosis (6), because it has a direct impact on morbidity, mortality, quality of life, and treatment decisions (5). The primary aim of treatment is to obtain an adequate platelet count(7). First- or second-line treatment strategies such as corticosteroids, intravenous immunoglobulin (IVig), and splenectomy may reduce the destruction of antibody-coated platelets, but their efficacy is limited (7). With immunosuppressive monotherapy, ITP patients often require long-term treatment, which sometimes leads to serious adverse effects. Studies involving short-term treatment with dexamethasone and rituximab have reported encouraging results. Adding cyclosporine to this combination targets T cells (8). The purpose of giving combination therapy includes the need for the effects of more rapid-acting agents and synergism between different agents until the effects of rituximab begin (1). The greatest progress in the treatment of ITP in the last decade has been the development of thrombopoietin receptor agonists (TPO-RA) (9). It provides many advantages over other drugs, especially in the elderly population. Comorbidities related to old age affect the course of the disease and responses to treatment (10). Treatment of chronic ITP is difficult, especially because of limited resources and treatment-related complications (11). Therefore, disease management depends on the clinician's decision and patient preference. In this study, we aimed to evaluate the efficacy and safety of the quadruple therapy consisting of oral dexamethasone, oral cyclosporine, and intravenous low-dose rituximab in addition to eltrombopag therapy.

MATERIAL AND METHODS

This study, which was planned retrospectively, included four patients who were diagnosed as having ITP in the hematology department of a tertiary care hospital from January 1, 2013 to December 31, 2020. This study obtained the approval from the ethics committee (Approval Date: 07.04.2021; Reference Number / Protocol No: 2021/07) and was done in accordance with the Declaration of Helsinki. In addition, written informed consent was obtained for all patients participating in the study.

Patients: Four patients who were diagnosed with ITP in our clinic who received IVig + steroid in the first-line treatment and eltrombopag in the second-line treatment, who could not achieve complete remission/partial remission included in the study. Patients with known HIV, hepatitis B or hepatitis C infections, malignant disease diagnosis, chemotherapy or radiotherapy and those with a diagnosis of myelodysplastic syndrome (MDS) or aplastic anemia were excluded from the study. Bone marrow aspiration and biopsy were performed in to rule out MDS and other causes of thrombocytopenia. Response to treatment was evaluated according to the platelet count (/mm³) and defined as complete response (>100,000/mm³), partial response (30,000-100,000/mm³ or doubling of platelet count after treatment), and unresponsive (<30.000/mm³).

RESULTS

IVig (1mg/kg/day iv 2 days) and steroid (dexamethasone 40 mg/day iv 4 days) were given as initial treatment in our four patients. No response was achieved in one of these patients. In the follow-up of our patients who responded to therapy, loss of response occurred in one of patient at the 3rd month, and in the other patients at the 6th and 12th months, and they were readmitted to the hospital with hemorrhage. The treatment with IVig and steroids was repeated in these patients. However, no response was achieved. Splenectomy could not be performed in two of our patients due to their age. One of our patients voluntarily refused to have splenectomy. One of our patients had a splenectomy due to ITP in childhood. Eltrombopag treatment was started in our patients who were unresponsive to steroid treatment and could not undergo splenectomy. The initial dose of eltrombopag was 50 mg; it is given as a recommended dose by the Turkish Ministry of Health. After 2 weeks of treatment, in those with platelet levels <30.000/mm³ the dose was increased 25 mg up to a maximum daily dose of 75 mg. However, no response was achieved. We added oral dexamethasone (40 mg/day 4 days), oral cyclosporine (2.5-3 mg/kg/day 28 days), and intravenous low-dose rituximab (100 mg/day iv 7, 14, 21, 28 days) to the eltrombopag 50 mg/day treatment. We did not give a loading dose for cyclosporine, we monitored weekly blood cyclosporine level for toxicity and titrated to a target dose of 200 to 400 μg/L. The demographic and clinical characteristics of our patients are shown in Table 1. No toxicity-induced death, serious treatment-related adverse events, or nonadherence to treatment were observed. The responses of the patients were summarized graphically in Figure-1.

Overall, the complete response rate at 6 months was 75% with quadruple therapy. In our 3 patients who received quadruple therapy partial

Table 1: Demographic and clinical characteristics of the patients.

Factors	Case-1	Case-2	Case-3	Case-4
Age/sex	51/male	68/female	58/female	32/female
Previous treatment	Methylprednisolone +IVig No splenectomy Eltrombopag	Methylprednisolone +IVig No splenectomy Eltrombopag	Methylprednisolone +IVig No splenectomy Eltrombopag	Methylprednisolone +IVig splenectomy Eltrombopag romiplostim
Bone marrow biopsy	(+)	(+)	(+)	(+)
Time from First Diagnosis to Quadruple therapy (TT4+eltrombopag)	12th month	3rd month	6th month	-
Response to Quadruple therapy (TT4+eltrombopag)	Complete response	Complete response	Complete response	No response
The final response status	after TT4+eltrombopag treatment was sustained with eltrombopag 50mg/day. Eltrombopag treatment was discontinued in the 24th month. The follow-up of the patient is continuing without medication.	after TT4+eltrombopag treatment was sustained with eltrombopag 50mg/day. The patient is still using eltrombopag 50mg/day PO.	Splenectomy (+) due to loss of response 6 months after the response to TT4+eltrombopag treatment. Currently using eltrombopag 50 mg po	No response She was referred to a clinical study.

IVig:Intravenous immunoglobulin; TT4: high-dose dexamethasone, low-dose rituximab, and cyclosporine; po:peroral

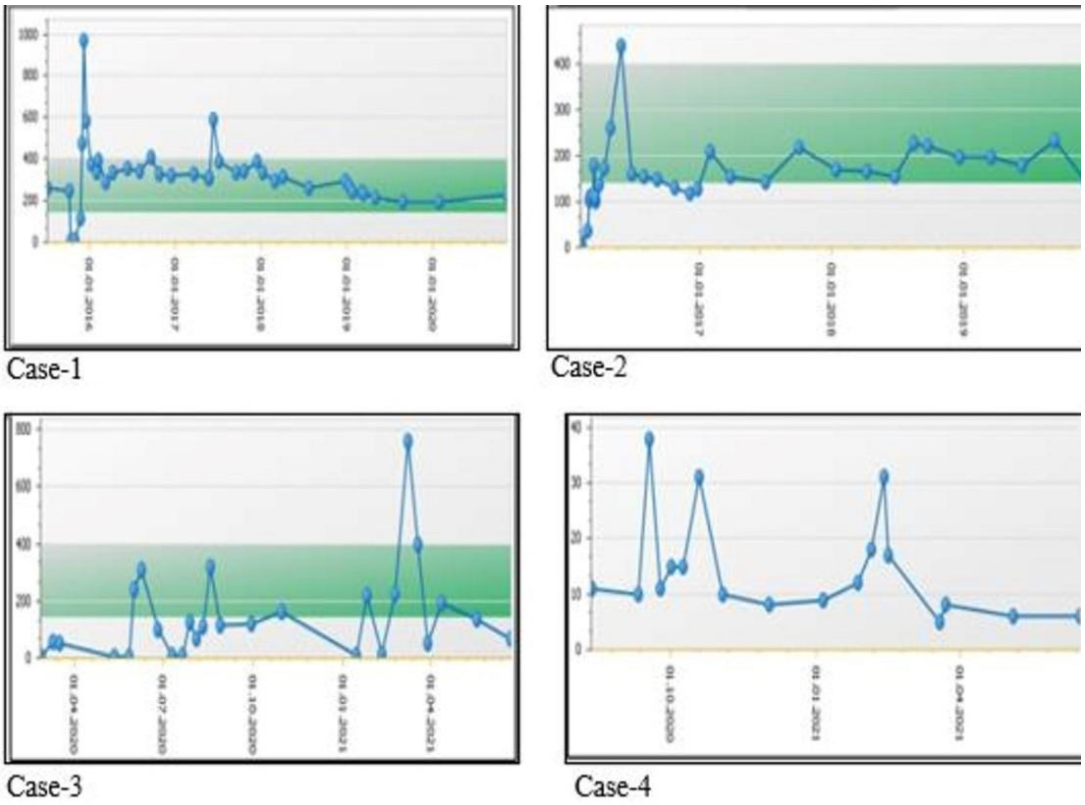

Figure 1. Graphs showing the responses achieved with quadruple therapy.

response (platelet 30000-100000/mm³) was achieved on the 14th day and complete response (>100000/mm³) was achieved on the 28th day. While our case-1 and case-2 patients are still being followed up by us with a complete response as of 2022, case-3 underwent splenectomy because of relapse after 6 months and is still being followed up with eltrombopag therapy. In case 4, which was unresponsive, romiplastim treatment was applied with an off-label application, but there was no response to this treatment either. The patient was referred to a clinical study.

DISCUSSION

The interpretation of our study is limited due to the small number of cases. Bone marrow examination is not diagnostic in patients with ITP, but it is recommended to be performed in patients with hematologic abnormalities and those who do not respond adequately to treatment (12). We also performed bone marrow aspiration and biopsy in our patients to exclude MDS and other hematologic pathology. Quadruple therapy was well tolerated by 4 of our patients, including the one who is over 65 years of age. Most of the treatment-related adverse events were grade-I and usually resolved in a short time. Excessive toxicity was not observed. Our study included 4 patients who had failed previous treatments (steroid, eltrombopag, splenectomy in one patient). Steroid resistance had increased significantly in all 4 patients who had previously received 2 lines of treatment. All of these cases were less likely to respond or recover spontaneously than previously untreated ITP patients (13,14). Although treatment with quadruple therapy was more successful in patients who failed <3 steps of treatment, longer duration of the disease was not a disadvantage; however, one of our patients did not respond to the treatment. Since CD4+ T cell activation is part of the pathogenic cycle that perpetuates ITP, suppressing their activation seems a resonable goal. Supportive of this hypothesis, cyclosporine monotherapy has been shown to be effective in chronic and refractory ITP (15). Rituximab (RTX), a chimeric monoclonal antibody against CD20, has been frequently used in the management of ITP and has been recommended as second-line therapy (1). Over the past decade, clinical trials on RTX have reported an initial response rate of 50-60% in ITP (16). Recent studies have shown that the response rate to low-dose RTX 100 mg once weekly for 4 weeks is similar to that of standard-dose RTX (375 mg /m² x 4) in ITP patients (17). Choi et al (8) reported in their study that platelet counts increased within 4 weeks after the start of treatment, and CD4+ counts decreased during this period. Although dexamethasone alone may cause T-cell suppression to a certain degree, they hypothesized that there might be a synergism with cyclosporine that may result in improved platelet responses, at least for a subset of ITP patients. Hanyin Wang et al (18) reported that they treated a 29-year-old male patient with severe ITP refractory to standard therapy, including steroid, IVig, and then splenectomy by using combination therapy of rituximab, romiplostim, and mycophenolate. Future studies are needed to evaluate the safety and efficacy of combining rituximab with TPO-RAs, and immunosuppression therapy in the postsplenectomy setting particularly for patients with refractory ITP. The response delay reported with low-dose rituximab can be improved by adding dexamethasone (15). In the study of Choi et al(8) the important advantage of TT4 (high-dose dexamethasone, low-dose rituximab, and cyclosporine) was that it provided long-term remission in 60% of the patients in a short time (28 days) without further treatment, and thus the results of the study were promising. Romiplostim and eltrombopag, which are TPO-RA, are increasingly used in the treatment of ITP. Previous studies have shown that both drugs are generally effective and safe in most ITP patients. However, serious adverse events such as thromboembolic events, arthralgia, increased bone marrow fibrosis, and myeloproliferative neoplasms have also been reporte d(19). Ahmad F et al (11) reported that TT4 was successful in their study that included 40 patients and the 6-month response rate was high. In several recent studies 375mg/m² weekly treatment of rituximab in combination with dexamethasone for 4 days has been shown to increase platelet counts in chronic ITP patients but not the risk of adverse effects. This combination is associated with higher platelet counts compared to dexamethasone monotherapy (18). Ahmad F et al(11), like Choi et al (8) suggested that lower doses of 100 mg weekly rituximab for 4 weeks may be beneficial for chronic ITP patients. Patient management is dependent on clinician decision and patient preference, given both the rarity of the condition and the lack of high-quality clinical trial evidence to inform practice guidelines. Based on these studies, we have also given TT4 treatment together with eltrombopag in our patients.

CONCLUSION

We found that the responses were long-term in three of our four cases. Our literature search revealed that this type of combination therapy is unique. Although our case number is low, our experience has shown that quadruple therapy can also be used as an option in ITP patients who are resistant to treatments. To assess the effectiveness and long-term results of this new combination treatment, prospective studies with a large number of cases are needed.

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