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THROMBOPOIETIN RECEPTOR AGONISTS IN THE TREATMENT OF PRIMARY IMMUNE THROMBOCYTOPENIA: OUR EXPERIENCE

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The primary immuna thrombocytopenia (ITP) is an acquired autoimmune disease characterized by isolated thrombocytopenia PLT < 100 x 10^9/L, and the absence of all conditions and diseases that can result in thrombocytopenia. The first-line therapy in ITP involves the use of corticosteroids, intravenous immunoglobulin or an immunoglobulin anti-D. The second-line treatment includes splenectomy, immunosuppressive drugs and agonists of thrombopoietin receptor (TPO-RA). To describe the treatment results with TPO-RA (eltrombopagin patients with ITP in the Clinic of Hematology UCC NIš. Between March 2018 and December 2023, at the Clinic of Hematology UCC Niš, 6 patients with ITP in which the previous treatment lines did not respond to the therapy or gave side effects were treated with TRO-RA. The indication for the TRO-RA therapy was chronic ITP. The period from the diagnosis to the initiation of the treatment with TRO-RA was on average 71,5 months. The analysis of the average number of platelets after TPO-RA therapy showed an upward trend. The TPO-RA does not show immunosuppression, they lead to an increase in platelet count, stopping bleeding and improving the quality of life. Therefore, TPO-RA are essential medicines for the treatment of ITP after the failure of the first and second - line therapy.

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Key words: *immune thrombocytopenia, treatment of immune thrombocytopenia, thrombopoietin receptor agonists*

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Introduction

Primary immune thrombocytopenia or idiopathic thrombocytopenic purpura (ITP) is an acquired autoimmune disease in which platelet destruction occurs under the action of primary antiplatelet antibodies against platelet glycoproteins GPIIb/IIIa, GPIb/IX. These antibodies not only coat platelets but also damage megakaryocytes (1–5).

There is also evidence that ITP is a disease of T lymphocytes (different subpopulations of CD4 T cells) where the loss of immune tolerance to self-antigens is thought to be a consequence of the formation of antibodies and cytotoxic T lymphocytes directed against the patient's own platelets and megakaryocytes. The activation of CD4 T cells can be an initial event in the development of ITP, which is reflected in B cells to produce antiplatelet antibodies (1, 4).

Idiopathic thrombocytopenic purpura is characterized by isolated thrombocytopenia, a platelet count of less than 100 x 10^9/L and the absence of all conditions and diseases that can lead to thrombocytopenia (1, 6).

ITP is more common in women aged 20 to 50 years who were generally healthy until then.

The International Working Group (IWG) defines ITP as: 1. newly diagnosed (the diagnosis established up to 3 months); 2. persistent (3 - 12 months from the diagnosis) or 3. chronic (lasting for more than 12 months) (1, 5). They also clearly defined severe and refractory ITP. Severe ITP is reserved for patients who have clinically relevant bleeding, defined as bleeding at the presentation of sufficient magnitude to mandate treatment or by the occurrence of new bleeding symptoms requiring additional interventions or an increase in drug dose. Refractory ITP is defined as the presence of severe ITP occurring after spleenectomy (7).

The goal of treating patients with ITP is to avoid serious bleeding, excessive treatment and maintain a normal quality of life. The treatment is initiated in patients with a platelet count of less than 30 x 10^9/L, as well as in patients with a higher platelet count who exhibit spontaneous bleeding or have an increased risk of bleeding (6, 8).

The first therapeutic line in the treatment of ITP is corticosteroids at a dose of 0.5−2 mg/kg body weight/day for 2−4 weeks, including a period of gradual reduction of the corticosteroid dose (9). The expected time to respond to the therapy is from a few days to a maximum of 4 weeks, while the use of corticosteroids is accompanied by many side effects such as corticosteroid dependence, diabetes, Cushing's disease, hypertension, gastric disturbances (1, 6, 9, 10, 11) .

The reticuloendothelial blockade is achieved by using intravenous immunoglobulins or anti RhD immunoglobulin in Rh-positive patients (6).

Intravenous IgG immunoglobulins are also an effective method of treatment and are administered at a dose of 1 g/kg/day for 1−2 days, or 0.4 g/kg/day for 5 days. The expected response time after the administration of intravenous immunoglobulins is 2−4 days, but they lead to a temporary increase in the number of platelets for 2−4 weeks. Due to the high cost and short-term effect, their use is limited to emergency cases, preparation for surgical interventions, and in cases where the use of corticosteroids is contraindicated (1, 10, 11).

Administration of anti-RhD immunoglobulin can cause reticuloendothelial blockade only in Rh-positive patients, using a higher dose of about 1.2 mg in adults. It gives a much faster therapeutic response (within a few minutes to a few hours) compared to IV immunoglobulins, but it can be less effective (1, 10, 11).

If no response is achieved with the first line of therapy, the treatment is carried out with the second line (1, 10, 11).

The second therapeutic line is spleenectomy with a frequency of long-term remission of up to 65%, lasting 5−10 years, while about 20% of patients relapse in the first two years. This type of treatment has a double effect, it removes the site of the breakdown of platelets coated with antibodies as well as the main site of the antibody synthesis. In the last 10 years, splenectomy has been performed less often, and the reasons are lifelong immunocompromise and new therapeutic modalities for the treatment of ITP (1, 5, 6, 10, 11).

The second therapeutic line includes immunosuppressive drugs, such as azathioprine, cyclophosphamide, vinblastine or vincristine, cyclosporine A, danazol, anti-CD20 monoclonal antibody and thrombopoietin receptor agonists (TPO-RA) (6, 7).

Thrombopoietin receptor agonists (TPO-RA) represent a new class of drugs in the treatment of ITP. Unlike other drugs for ITP, which achieve their therapeutic effect by reducing the production of antibodies and reducing the breakdown of platelets, TPO-RA stimulate megakryocytopoiesis (5, 12). This group of drugs includes eltrombopag (Revolade) and romiplostin (N-PLATE) (13) which are recommended for patients resistant to conventional treatment, i.e. the first line of therapy, or splenectomy (9). Eltrombopag is a small peptide molecule that exerts its effect by activating the same signalling pathways as endogenous thrombopoietin, stimulates the proliferation and differentiation of megakaryocytes and their precursors and thus leads to an increase in the number of platelets, cessation of bleeding and improvement in the quality of life in 80% to 90% of patients with chronic ITP (4, 12, 14, 15, 16). It is administered orally, in a dose of 25−75 mg daily and the therapeutic response is achieved after 1 to 5 weeks from the beginning of the administration. The most common adverse reactions (headache, weakness, arthralgia, elevated transaminase values, bone marrow fibrosis, thrombosis, etc.) are mild to moderate (2, 14, 16). Sometimes they can cause renal weakness, which requires screening of kidney function (9).

Aim

The aim of the study was to present the treatment results of patients with ITP using TPO-R agonists in the Clinic of Hematology, Allergology and Clinical Immunology.

Material and Methods

Six patients with chronic ITP, with no response to the previous therapeutic lines and without side effects, were treated using eltrombopag, at the Clinic of Hematology, Allergology and Clinical Immunology from March 2018 to December 2023. No patient was spleenectomized. Since 2017. patients have been treated at the expense of the Republic Health Insurance Fund.

The criteria for chronic and refractory ITP are defined by the recommendations of the IWG.

The TPO-R agonist (eltrombopag) was administered in the range of 25 mg to 75 mg orally, daily with a permissible dose escalation up to 75 mg or dose reduction up to 25 mg according to recommendations. The dose of eltrombopag is individual, adapted to each patient, in order to achieve and maintain the number of platelet count above 50 x 10^9/L for at least 4 weeks with the aim of reducing the risk of bleeding (1, 8, 10).

The treatment was initiated at a platelet count of less than 20−30 x 10^9/L, as well as in patients with a higher platelet count who exhibited spontaneous bleeding or had an increased risk of bleeding. Patients were prohibited from using aspirin, non-steroidal anti-inflammatory drugs, intramuscular injections and inappropriate physical activity (8).

The drug was administered 2 hours before or 4 hours after a meal while avoiding foods with a high calcium content. During the therapy, it was necessary to control the blood count once a week until the platelet count reached above 50 x 10^9/L, and then once a month with regular control of transaminases and bilirubin. After 2 weeks of starting therapy with eltrombopag, the number of platelets increased, and after the termination of the treatmentafter 1 to 2 weeks the number of platelets decreased.

The response to the therapy was defined as CR-complete response (a platelet number greater than 100 x 10^9/L and the absence of bleeding); PR-partial response (a platelet count greater than 30 x 10^9/L with the absence of bleeding) or no response (a platelet count less than 30 x 10^9/L, with hemorrhagic syndrome and/or corticosteroid dependence (1). A stable increase in platelets > 50 x 10^9/L was considered a good therapeutic response (13, 17).

Results

Six patients with ITP were treated with eltrombopag, out of whom 2 (33%) were male and 4 (67%) were female (Figure 1).

The average age of all patients at the time of starting eltrombopag therapy was 45.6 years. The youngest patient was 22 years old, and the oldest was 70 years old.

The indication for the introduction of TPO-RA therapy (eltrombopag) was chronic ITP. Three patients previously used 4 therapeutic lines (corticosteroids, azathioprine, cyclophosphamide, vinca alkaloids), two patients used 2 therapeutic lines (corticosteroids and azathioprine), and one patient used 3 therapeutic lines (corticosteroids, azathioprine, cyclophosphamide) (Table 1).

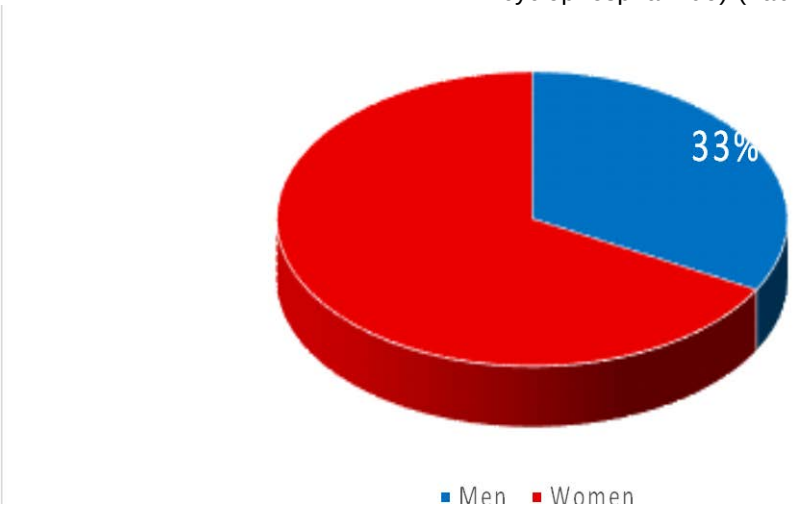

Figure 1. Patients with primary immune thrombocytopenia by gender

Table 1. Previous lines of therapy in patients with primary immune thrombocytopenia

Patients with ITP	Splenectomized patients	Therapeutic lines before the introduction of eltrombopag
1.	No	Corticosteroids Azathioprine
2.	No	Corticosteroids Azathioprine Cyclophosphamide Vinca alkaloids
3.	No	Corticosteroids Azathioprine Cyclophosphamide Vinca alkaloids
4.	No	Corticosteroids Azathioprine
5.	No	Corticosteroids Azathioprine
6.	No	Corticosteroids Azathioprine Cyclophosphamide

The time from diagnosing ITP to the initiation of the TPO-RA therapy was, on average, 71.5 months (range 24−144) (Figure 2) and number of platelets at the time of introduction of TPO-RA was 21 x 10^9/L (range 8−33).

In one patient, the treatment started with eltrombopag at a dose of 25 mg per day, and after six months the dose was increased to 50 mg by the number of platelets; in two patients, the treatment was carried out with a dose of eltrombopag 50 mg, which was maintained during the duration of the therapy; in three patients, the treatment started with 50 mg of eltrombopag and the dose was increased to 75 mg after six months, while in one of them, in addition to the increase of the drug dose, corticosteroid therapy was also included.

The response time after the inclusion of eltrombopag was 4 to 6 weeks.

The average length of eltrombopag administration was 38.16 months (range 3−69 months), and the average platelet count for that period was 79.12 x 10^9/L (range 13 −333 x 10^9/L).

The analysis of the average number of platelets after the introduction of TPO-RA showed the following trend: for the first patient, the average number of platelets was 122 x 10^9/L (range 33−189); for the second patient, the average number of platelets was 91 x 10^9/L (range 28−141); for the third patient, the average number of platelets was 24.1 (range 8 −71); for the fourth, the average number of platelets was 88.4x10^9/L (range 28−223); for the fifth patient, the average number of platelets was 73.9 x 10^9/L (range 13−333); for the sixth patient, the average platelet count was 75.3 x 10^9/L (range 16−139) (Table 2).

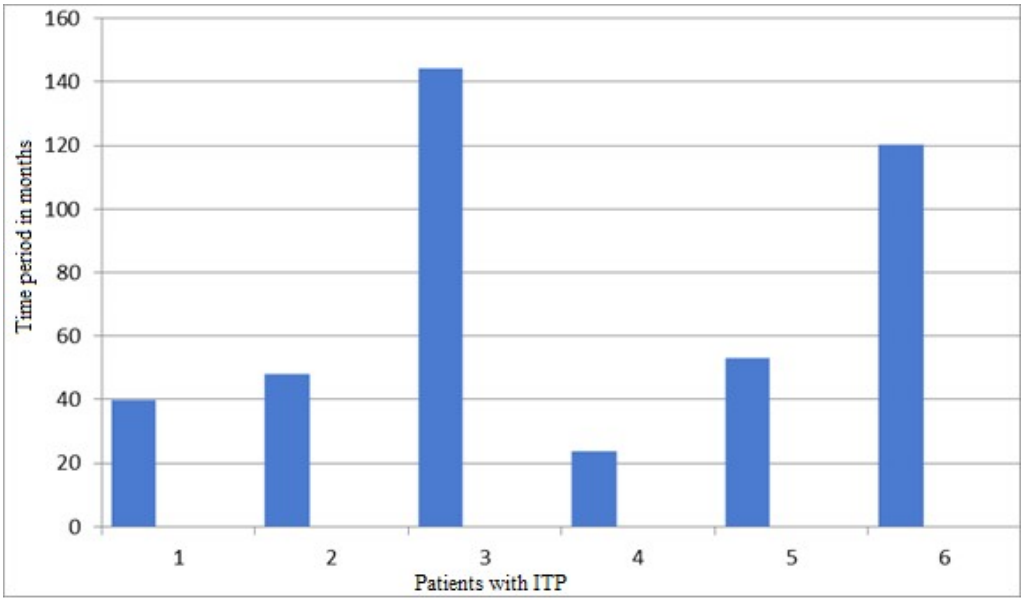

Figure 2. Time period in months from diagnosis of ITP to initiation of therapy with thrombopoietin receptor agonists

Table 2. Effect of eltrombopag therapy in patients with primary immune thrombocytopenia

Patients with ITP	Platelet count before eltrombopag administration	Platelet count after eltrombopag administration	Concomitant therapy	Side effects
1.	33x10^9/L	189X10^9/L(CR)	Without therapy	No
2.	28x10^9/L	149X10^9/L(CR)	Without therapy	No
3.	8x10^9/L	71X10^9/L (CR)	Corticosteroids	No
4.	28x10^9/L	223X10^9/L	Without therapy	No
5.	13x10^9/L	333x10^9/L	Without therapy	No
6.	16x10^9/L	139x10^9/L	Without therapy	No

The patients showed good therapeutic response; 5 patients completely responded to the included therapy, except for one patient who showed a partial response, but without hemorrhagic syndrome (in the absence of bleeding).

There were no unwanted effects during the administration of the drug.

Discussion

Immune thrombocytopenia is a disease that is more common in women (17), with a median age at the time of diagnosis of 56 years, with an incidence that increases with age. In our small group of patients, the median age was 45.6 years.

The aim of ITP treatment is to achieve a stable number of platelets that prevent the development of bleeding. TPO-R agonists are second-line drugs for the treatment of chronic ITP. The effect is manifested from of 2 to 5 weeks from the beginning of the application, in our group of patients from 4 to 6 weeks, which corresponds to the data from the literature (17, 18). Eltrombopag is well tolerated, and the most common adverse reactions are headache, nausea, and nasopharyngitis. Reversible increase in transaminases may occur, although no adverse reactions were recorded in our small group of patients.

All our patients responded to the therapy with a good therapeutic response after 4 to 6 weeks. In one patient, a stable response was maintained by adding corticosteroids. In one patient with a platelet count above 200 x 10^9/L, the dose was reduced to 25 mg, and the possibility of discontinuation of therapy or maintenance therapy was considered. The well-known data in the literature are that in most patients, discontinuation of TPO-R therapy leads to relapse of the disease, but about 20% maintain remission I after discontinuation of therapy (19).

Conclusion

The second-line therapeutic modalities available in Serbia for the treatment of chronic ITP are few (azathioprine, cyclophosphamide, vinca alkaloids), and treatment results are variable and unpredictable (therapeutic response 30−35%), and side effects are numerous. The efficacy and safety of drugs second-line have not been verified in randomized, double-blind, placebo-controlled studies (8, 10). TPO-R agonists do not show immunosuppression, they activate the same signaling pathways as endogenous TPO and lead to an increase in the number of platelets, cessation of bleeding and improvement in quality of life (17, 18). Their efficiency is 80−90% and they are well tolerated. For this reason, TPO-R agonists are necessary drugs for the treatment of ITP after the failure of the first and second line of therapy (16, 18).

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AGONISTI TROMBOPOETINSKIH RECEPTORA U LEČENJU PRIMARNE IMUNSKE TROMBOCITOPENIJE: NAŠE ISKUSTVO

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Primarna imunska trombocitopenija (ITP) jeste stečena autoimuna bolest koja se odlikuje izolovanom trombocitopenijom Tr < 100 x 10^9/L i odsustvom svih stanja i bolesti koje mogu dovesti do trombocitopenije. Prva terapijska linija podrazumeva primenu kortikosteroida, intravenskih aplikovanih imunoglobulina ili anti-D imunoglobulina. Druga terapijska linija obuhvata splenektomiju, imunosupresivne lekove i agoniste trombopoetinskih receptora (TPO-RA). Cilj ove studije bio je da prikaže rezultate lečenja bolesnika sa ITP-om koji su na Klinici za hematologiju Univerzitetskog kliničkog centra u Nišu lečeni agonistima trombopoetinskih receptora (eltrombopagom). U periodu od marta 2018. do decembra 2023. godine primenom eltrombopaga lečeno je šest bolesnika sa ITP-om kod kojih je došlo do izostanka odgovora na prethodne linije terapije ili do ispoljavanja neželjenih efekata. Indikacija za uvođenje eltrombopaga bio je hronični ITP. Vreme od postavljanja dijagnoze ITP-a do otpočinjanja terapije TPO-RA iznosilo je u proseku 71,5 meseci. Analiza prosečnog broja trombocita po uvođenju TPO-RA pokazala je trend porasta broja trombocita, bez neželjenih efekata. Agonisti TPO-RA ne pokazuju imunosupresiju, dovode do porasta broja trombocita, prestanka krvarenja i poboljšanja kvaliteta života. Upravo zato, agonisti TPO-RA predstavljaju neophodne lekove za lečenje ITP-a posle neuspeha prve i druge terapijske linije.

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***Ključne reči**: imunska trombocitopenija, terapija imunske trombocitopenije, agonisti trombopoetinskih receptora*