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COMPARATIVE EVALUATION OF NEW TREATMENTS FOR IMMUNE THROMBOCYTOPENIA

[1]Kattabek M. Abdiev , [2]Ozoda G. Madasheva , [3]Oyzhamol N. Ruziboeva , [4]Khudoyor M. Shomirzaev

[1]Associate Professor Samarkand Medical Institute Samarkand, Uzbekistan

[2]Senior Lecturer Samarkand Medical Institute Samarkand, Uzbekistan

[3]Assistant Samarkand Medical Institute Samarkand, Uzbekistan

[4]Assistant Samarkand Medical Institute Samarkand, Uzbekistan

Abstract:

The article gives a brief overview of what disease is immune thrombocytopenia, the causes of its origin. Treatment methods were also analyzed and their level was studied. A brief critical evaluation was given for immune thrombocytopenia (ITP) based on a firm and direct assessment of the first and course of treatment. Based on the objective data tested in high-quality clinics, it was concluded that it was necessary to introduce new treatment strategies with better efficacy.

Key words: immune thrombocytopenia, platelet, platelet transfusion, splenectomy, romiplostim, eltrombopag, vincristine, cyclophosphamide, azathioprine, dapsone, cyclosporin A, mycophenolate mofetil, and rituximab.

Introduction:

Immune thrombocytopenia is a disorder in which antibodies form that destroy platelets in the body. The cause of the antibody formation is unknown; however, in children, ITP often occurs after a viral infection. Bone marrow can increase platelet production to compensate for the destroyed elements, but this is usually not enough. Sometimes antibodies that destroy platelets also attack the bone marrow and cause a decrease in platelet production.

In adults, ITP is usually long-term (chronic). Children often self-resolve ITP.

The goal of treating patients with ITP is to reduce the risk of severe bleeding and achieve a sustained response to therapy. However, it is currently not possible to personalize the choice of therapy. The reason, mainly, lies in the imperfection of the treatment algorithm and, first of all, in the absence of criteria for predicting the effectiveness of therapy. When choosing a method of treatment, there is no principle of individualization, which would be focused on the patient's status (gender, age, lifestyle, concomitant diseases) and the characteristics of the course of the disease (hematological parameters, severity of HS, biological phenotype). A reflection of this is the recommendatory nature of the guidelines for the treatment of ITP, which suggest changing the lines of therapy according to the nature of the response to previous treatment [21;15]. As a result, the choice of the method of therapy and the timing of initiation of treatment occur empirically, which is often accompanied by the formation of resistant variants of the disease and the patient's disability.

The main results and findings

To solve the set tasks, the following methods were used: descriptive method, interpretation method, method of conceptual analysis, method of thematic systematization. Clinical laboratory, molecular genetics and statistical methods were used in the work.

The results of the study provided additional information, which was the basis for the development of an algorithm for the diagnosis and treatment of patients with immune thrombocytopenia.

The goal of treating patients with ITP is to achieve a sustained response. In this regard, identification of indicators associated with the risk of an unfavorable course of the disease and predicting the effectiveness of treatment is of fundamental importance. In contrast to congenital hemostasis abnormalities (Glanzmann and Bernard-Soulier's disease), with ITP, there is no unambiguous

understanding of the role of the genotype in the development of the disease, the formation of the severity of HS and the response to treatment, including persistent response and resistance to therapy. Insufficient knowledge of the association of response with clinical parameters and AP variant of genes involved in the pathogenesis of ITP justifies the need for further research in order to optimize the diagnosis and treatment of this disease.

Immune thrombocytopenia is a disorder characterized by a blood abnormality called thrombocytopenia, which is a shortage of blood cells called platelets that are needed for normal blood clotting [21].

In ITP, the immune system makes antibodies against a person's own platelets and destroys them.

- People may develop small purple spots on their skin (petechiae) and bleed frequently.
- The diagnosis is made with a blood test by determining the number of platelets.
- Corticosteroids or other drugs are given to prevent platelet destruction.
- Some patients benefit from drugs that increase platelet production.
- In adult patients, doctors sometimes remove the spleen.

Platelets are cells produced in the bone marrow that circulate in the bloodstream and help blood clot. Typically, the blood contains approximately 140,000–440,000 platelets per microliter (140 x 109 per liter to 440 x 109 per liter). If the platelet count is reduced to about below 50,000 platelets per microliter (below 50x109 per liter) of blood, then even relatively minor injuries can cause bleeding. However, the most serious risk of bleeding in most cases occurs only when the platelet count drops to 10,000–20,000 per microliter (10 x 109 to 20 x 109 per liter) of blood. This is a very low level at which bleeding can occur without any noticeable damage.

Some people may not have symptoms. In others, symptoms of immune thrombocytopenia may develop suddenly or gradually. Fatigue is a common symptom in chronic ITP.

The first sign of a low platelet count may be bleeding from the skin. Often, a large number of tiny red dots (petechiae) appear on the skin of the legs, and even minor lesions can cause bluish-black bruising (ecchymosis or purpura). Gums may bleed; blood may appear in stool or urine. Menstruation or nosebleeds may be more severe than usual. Sometimes this bleeding is difficult to stop.\

The bleeding increases as the platelet count decreases. People with very low platelet counts can lose a lot of blood that goes into their digestive tract; they can also develop life-threatening bleeding in the brain, even if no injury is present. With a hemorrhage in the brain, headache may occur.

Diagnostics of ITP:

- Blood tests to determine platelet count and clotting
- Tests to rule out other conditions that lead to low platelet count and bleeding

Doctors diagnose immune thrombocytopenia (ITP) if the platelet count is less than 100,000 per microliter (less than 100 × 109 per liter) of blood without a similar decrease in red blood cells or white blood cells, and if there is no other clear explanation for thrombocytopenia, such as infection or use of certain drugs (see Table Causes of thrombocytopenia). There is no reliable survey to confirm ITP.

Microscopic examination of a blood sample or automated platelet count should be done to determine the severity of thrombocytopenia and to identify the cause of the disease. It is necessary to conduct a microscopic examination of blood for the differential diagnosis of ITP, thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). TTP and HUS are also diseases that can cause thrombocytopenia due to the destruction of platelets.

In rare cases, a bone marrow sample (bone marrow biopsy and aspiration) is taken and examined under a microscope to obtain information about platelet production.

ITP treatment:

- Corticosteroids
- Intravenous immunoglobulin, thrombopoietin receptor agonists, or other immunosuppressants (eg, rituximab, azathioprine, or mycophenolate)
- Sometimes removing the spleen
- Rarely, platelet transfusion

In ITP, antibodies that destroy platelets may be temporarily blocked with corticosteroids (such as prednisone) or intravenous immunoglobulin to increase platelet count. Typically, after such treatment, children recover within a few weeks or several months.

Some adults recover within the first year, but most do not recover from the disease. Adults who do not respond well to corticosteroids may need to take additional drugs that increase platelet production (thrombopoietin receptor agonists) or suppress the immune system, including rituximab, azathioprine, Cytoxan, cyclosporine, or mycophenolate mofetil. Fostamatinib is a new drug that can be used when other drugs have failed.

Thrombopoietin receptor agonists (eg, romiplostim, and avatrombopag) increase platelet production and can be effective for many years. These medications are especially useful for people who are unable or unwilling to undergo spleen removal.

Some adults (but usually not children) with ITP end up having to have their spleen removed surgically (splenectomy) to increase their platelet count. Disadvantages of splenectomy include an increased risk of blood clots, an increased risk of malignant tumors, and an increased risk of certain life-threatening infections. People who have a splenectomy may be given certain antibiotics or vaccines that reduce (but do not completely eliminate) the risk of infection. Drug treatment is increasingly being used instead of splenectomy.

For life-threatening bleeding, platelet transfusion (in addition to intravenous corticosteroids and / or immunoglobulin) may be given.

The consistency in prescribing different treatments for ITP is defined as a line of therapy.

The main therapeutic goal in ITP is to carry out the minimum necessary therapeutic measures to maintain a platelet level sufficient to eliminate hemorrhagic syndrome (more than 30 × 109 / L) with the least number of side effects [15, 15]. In the American Society of Hematology guidelines, a platelet count of 30-50 x 109 / L with no other risk factors is considered sufficient to prevent serious complications of ITP (intracerebral or severe gastrointestinal bleeding), and a platelet count above 50 x 109 / L is defined as "safe" for implementation of invasive interventions [14,16].

Various research groups and clinical guidelines recommend glucocorticosteroids (GCS) as first-line therapy [14, 17].

Prednisolone 0.5–2 mg / kg / day is the generally accepted starting dose for patients with ITP. After the platelet count reaches 50 × 109 / L, it is recommended to reduce the dose to the minimum effective, sufficient to maintain the platelet level at the level of 30-50 × 109 / L. One to four cycles of dexamethasone 40 mg / day for 4 days is the predominant regimen for prescribing GCS with a response rate of 50–80% in adult patients with newly diagnosed ITP [3, 19]. According to the international cosensus dedicated to the research and treatment of ITP, prednisolone, dexamethasone, or methylprednisolone are equally acceptable as first-line therapy [14]. With resistance to GCS, the duration of therapy should not exceed 4 weeks.

Intravenous immunoglobulin and anti-rhesus immunoglobulin (anti-D) are effective for increasing platelet count, but the effect is usually transient. These drugs are recommended as first-line therapy in emergency situations [7, 21].

For patients with chronic ITP who have not responded to corticosteroids or have serious side effects, splenectomy is recognized as a second-line therapy. However, approximately 15–20% of patients do

not respond to splenectomy and another 15–20% of respondents develop relapses after weeks, months or years [16, 23]. In addition, many patients with chronic ITP refuse splenectomy due to possible complications such as bleeding, infection, thrombosis, and the risk of death (0.2–1.0%). [10]
There is worldwide experience with the use of vincristine, cyclophosphamide, azathioprine, dapsone, cyclosporin A, mycophenolate mofetil, and rituximab in patient's refractory to splenectomy, recurrent after splenectomy, or contraindicated to surgery. The response rate for the above types of therapy ranged from 20 to 80%. However, most studies evaluating the effectiveness of immunosuppressive drugs have not been randomized, which suggests that a strong evidence base for the effectiveness and safety of such prescriptions is insufficient. In addition, their long-term use can be accompanied by serious side effects, in particular the development of secondary tumors and infectious complications.
Thus, in a prospective phase II clinical study in patients with ITP, the use of rituximab at a dose of 375 mg / m2 weekly for 4 weeks allowed a platelet count of 50 × 109 / L and higher in one third of patients [8]. In a study by N. Cooper et al. revealed the achievement of stable complete or partial remission in one third of patients, however, a long relapse-free period was not recorded [4]. Rituximab currently has no approved indication for the treatment of chronic ITP. According to Fianchi et al., Rituximab can cause fulminant hepatitis in carriers of hepatitis B, therefore its use is contraindicated in patients with active hepatitis B [6]. In addition, more than 50 cases of progressive multifocal leukoencephalopathy associated with rituximab have been reported in patients with lymphoma and systemic lupus erythematosus [1].
Before rituximab can be recommended as a standard therapy for ITP, it is necessary to obtain the results of additional studies to assess its efficacy and safety in this pathology.
The traditional first-line treatment for ITP is therapy with corticosteroids (CS) such as prednisolone, dexamethasone, methylprednisolone. However, long-term use of CS often causes the development of such undesirable phenomena as erosive lesions of the gastrointestinal tract, Itsenko-Cushing's syndrome, decreased glucose tolerance, depression, etc., which in most cases limits their long-term use. In addition, cases of ineffectiveness of first-line therapy are quite common.
In the presence of contraindications to the use of CS, as well as in case of urgent situations (high risk of life-threatening bleeding), therapy with intravenous immunoglobulin preparations is recommended, however, the response to this therapy is usually temporary.
In cases of ineffectiveness or loss of response to first-line therapy, splenectomy (removal of the spleen), thrombopoietin receptor agonists (aTPO-r) such as romiplostim or eltrombopag, and rituximab are offered as treatment options for the second or more lines of therapy.
Eltrombopag is the first oral low molecular weight synthetic non-peptide agonist of the thrombopoietin receptor registered in Belarus [5]. The drug has good oral bioavailability with a peak plasma concentration in 2–6 hours and a half-life of 21–32 hours [13]. The mechanism of action of eltrombopag is to increase platelet production by inducing proliferation and differentiation of bone marrow precursors of the megakaryocytic line. It has a high affinity for human plasma proteins (> 99%). Unlike native thrombopoietin, which binds to the extracellular domain of the thrombopoietin receptor, eltrombopag selectively binds to the transmembrane region of the receptor and does not compete with endogenous thrombopoietin. The drug is indicated for splenectomized patients with ITP who are refractory to other treatments (eg, corticosteroids, immunoglobulins). The recommended starting dose of eltrombopag is 50 mg once daily. If there is no increase in platelet count after 2-3 weeks of admission, the dose may be increased. After reaching a steady platelet level, the dose should be further adjusted to the lowest level to maintain platelet levels around 50 × 109 / L with minimal hemorrhagic manifestations.
Approximately 10% of patients receiving eltrombopag in the studies analyzed above had a three-fold increase in ALT compared with the upper limit of normal, compared with 3% in the placebo group (p>

0.05). In these patients, elevated ALT levels returned to normal while taking eltrombopag or shortly after discontinuation. In the EXTEND study, episodes of increased bilirubin were noted due to the indirect fraction, which is not an indicator of severe liver damage.

Thus, there is currently no clinical evidence that eltrombopag at the recommended dose can cause severe, irreversible liver damage. However, liver function tests should be performed regularly and, if there is a progressive increase in serum aminotransferases, the drug should be discontinued.

In the RAISE study, three patients (2%) who received eltrombopag developed therapy-related thromboembolic events. All three patients had risk factors for the development of venous thrombosis and the platelet count during the period of thrombotic events was less than 50 × 109 / L [2]. In the EXTEND study, 16 patients (5%) developed 20 confirmed thromboembolic events; deep vein thrombosis (n = 9) and cerebrovascular thrombosis (n = 5) were the most common.

Thus, the data of world studies do not allow us to conclude that there is a significant increase in the risk of thromboembolic complications when using eltrombopag. However, in patients with known risk factors for thrombosis, eltrombopag should be used with caution, with careful monitoring of the platelet count and the condition that the minimum platelet level is sufficient to stop the hemorrhagic syndrome.

Splenectomy (SE), which is statistically effective in 60% of cases, can cause severe postoperative complications (bleeding and thrombosis), especially in elderly patients. Removing the spleen leads to a high risk of developing severe bacterial infections of a certain type, which requires preventive vaccination and revaccination. This creates additional inconvenience and reduces the patient's quality of life.

The aTPO-r therapy has an acceptable safety profile. Side effects, such as headache, arthralgia, fatigue, are usually minimal, the frequency of their development is extremely low, and in general, side effects in the treatment of aTPO-r do not require its cancellation. However, if the patient is prescribed therapy with aTPO-r, it is usually administered for life, and the cost of aTPO-r is very high.

Rituximab is currently not approved for the treatment of ITP patients. Its use is possible only by decision of the medical commission, in the presence of vital indications and the consent of the patient. Previously widely used immunosuppressive drugs (danazol, azathioprine, mycophenolate mofetil, cyclosporin A), due to their high toxicity and low efficacy, are recommended only as reserve drugs for ITP therapy.

Until now, the choice of a particular type of therapy has been empirical. There were no clear prognostic markers of the course of ITP, response to therapy, and disease outcomes. The unpredictability of the response to therapy, the imperfection of traditional methods of ITP treatment due to the high incidence of side effects, as well as the high cost of modern drugs (for example, aTPO-r), dictate the need to search for the choice of the optimal treatment method.

The problems and limitations noted above in the management of patients with ITP necessitated the search for new drugs with a better profile of proven efficacy and safety, including those based on new pathophysiological and pharmacological approaches. According to the results of numerous studies, impaired platelet production is observed in many patients with ITP [9, 35]. Therefore, stimulation of megakaryocytopoiesis by thrombopoietin or thrombopoietin-like agents can be pathogenetically justified in the treatment of ITP. The use of recombinant thrombopoietin demonstrated the possibility of increasing platelet count in patients with ITP [12,36], but was associated with the production of autoantibodies that neutralize endogenous thrombopoietin, thereby leading to severe thrombocytopenia. In the early 2000s, two thrombopoietin receptor (TPO-R) agonists, romiplostim and eltrombopag, were licensed for the treatment of chronic ITP.

Conclusion:

According to world studies evaluating various methods of treating patients with chronic ITP, only two methods have high proven efficacy: splenectomy and conservative treatment with thrombopoietin receptor agonists. However, the risk of surgery, postoperative complications, and the lifelong risk of infection, limit the use of splenectomy. Thus, eltrombopag, the first representative of thrombopoietin receptor agonists, registered in the Republic of Belarus and recommended for the treatment of chronic ITP in patients with insufficient response to previous therapy, opens up new treatment options for this complex contingent of patients based on rigorous evidence-based medicine.

The main advantages of conservative treatment with eltrombopag are pronounced clinical efficacy (up to 80%) and high safety, including the absence of immunosuppressive or malignant effects, confirmed in high quality controlled randomized trials.

In addition, important positive properties of this new strategy for the treatment of ITP are the possibility of oral administration once a day, a stepwise increase or decrease in the dose if clinically necessary, and the lack of evidence of a decrease in efficacy with long-term administration. However, given the high cost of this new pharmacotherapeutic approach, the world's leading experts for pharmacoeconomic reasons, they recommend an individual approach to the tactics of managing patients with ITP, based on a thorough assessment of the clinical situation and patient needs, taking into account the latest scientific data and considering all modern treatment options, including thrombopoietin receptor agonists.

In this regard, I would like to draw the attention of specialists that in the majority of patients responding to therapy with eltrombopag, the number of platelets begins to increase after the first week of therapy and reaches a peak in the second week, i.e., this strategy is not a means of providing urgent care and emergency treatment. At the same time, eltrombopag can be used to induce remission in the preparation of patients with chronic ITP 2 weeks before the planned surgery.

The presented modern scientific information allows us to make informed decisions on the inclusion of the innovative drug eltrombopag (Revolide) in the national standards for the observation and treatment of ITP, with their subsequent updating as new data become available.

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