iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 10 **Issue:** VI **Month of publication:** June 2022

DOI: https://doi.org/10.22214/ijraset.2022.43924

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 10 Issue VI June 2022- Available at www.ijraset.com

The Effectiveness of The Treatment of Idiopathic Thrombocytopenic Purpura with Modern Drugs

Madasheva Anajan Gazkhanovna[1], Salimov Akmaljon Fatullo Ugli[2], Chorieva Lobarkhon Zayniddin Kizi[3]
[1]*Senior Lecturer of the department of Hematology, Samarkand State Medical University*
[2]*Student of medical faculty of the Samarkand State Medical University*
[3]*Student of medical faculty of the Samarkand State Medical University*

***Abstract:** This article discusses the effectiveness of treatment of idiopathic thrombocytopenic purpura with modern drugs and its new methods. Primary immune thrombocytopenia, commonly referred to as idiopathic thrombocytopenic purpura (ITP), is an acquired autoimmune disease characterized by isolated thrombocytopenia.*
***Keywords:** treatment, idiopathic thrombocytopenic purpura, modern drugs, new methods, clinical fetures, disease.*

I. INTRODUCTION

The classification of ITP can be based on the age of the patients (ITP in adults and ITP in children) and the duration of the disease (acute and chronic). The clinical features of ITP in adults differ from the course of ITP in children. In children, the disease often begins acutely, usually 2–3 weeks after a viral infection or immunization. While adults are characterized by a latent onset without previous viral or other diseases and a primary chronic course. When calculating the frequency of occurrence, the threshold platelet value is less than 50•109/l. From 1.6 to 3.2 cases of ITP development per 100,000 population are recorded annually. The median age among adult patients with ITP is 56 years [6]. In children, according to our data, the peak of the disease occurs at the age of 1–6 years (59%) and 12–15 years (28%), which is associated, firstly, with the vaccination schedule and intensive vaccination of children of this age, and, Secondly, with an increase in the incidence of infectious diseases in children due to the peculiarities of the immune response of the child's body during these age periods, the so-called "critical periods of the immune system".

II. MAIN PART

The disease is equally common in both males and females. More often, ITP in adults is diagnosed incidentally during a clinical blood test. Individuals with known thrombocytopenia in the range of 100-150•10 9/L who do not experience a further decrease in platelet count within 6 months are considered unlikely to worsen the disease, but it is not clear whether they have a greater risk in the future compared to the population as a whole for the development of other autoimmune diseases [8.p.1-10]. In adults, the clinical symptoms and course of ITP are varied - from completely asymptomatic to severe, with severe bleeding from various organs up to intracranial hemorrhage. In children, as a rule, ITP begins acutely and manifests itself with a pronounced clinical picture (skin hemorrhages, bleeding) against the background of significant thrombocytopenia <50•109/l.

Pathophysiology of ITP Although the etiology of ITP has not yet been definitively established, progress has been made in recent years in understanding the pathogenesis of ITP. The notion that ITP occurs solely due to the appearance of antiplatelet antibodies (AT), accompanied by increased destruction of platelets, has been challenged in the course of modern clinical and experimental studies. A more complex mechanism of platelet destruction involving T-lymphocytes, which play a significant role in this process, has been identified. The role of B-lymphocytes. Studies conducted by Harrington in 1951 for the first time showed that the destruction of platelets in ITP is caused by certain plasma factors, later called antiplatelet antibodies. Usually, in most patients, antiplatelet antibodies directed to glycoproteins (GP) of class IIb/IIIa and Ib/IX are identified [6]. However, it should be noted that in 50% of patients with ITP, antiplatelet antibodies are not detected, and, in addition, recovery from ITP can be observed despite the presence of an elevated level of antiplatelet antibodies in patients. The role of T-lymphocytes. T-lymphocytes also appear to be involved in the pathogenesis of ITP. A number of studies have shown that the production of antiplatelet antibodies by B-lymphocytes requires the assistance of specific antigens of CD4+ T-lymphocytes (helpers). Platelet-reactive T-lymphocytes were found in the blood of patients with ITP; the target of these cells was GP IIb/IIIa. In patients, AT synthesis was noted after exposure of T-lymphocytes to GP IIb/IIIa, and not after exposure to native proteins. The in vivo differentiation of these unknown epitopes and the reason for this persistent T cell activation remain unclear.

Presumably, these epitopes, as a rule, are not detected by the immune defense forces and can be detected by the immune system only under certain circumstances, for example, during infection. Another evidence of the involvement of T-lymphocytes, according to studies, is the fact that patients with chronic ITP quite often have an increase in the number of HLA-DR + T-lymphocytes, as well as an increase in the number of interleukin 2 receptors, an increase in the Th1 / Th2 ratio and an increase in monoclonal T-lymphocytes. Finally, in patients with ITP, an increase in the number of CD3+T lymphocytes involved in cell-mediated cytotoxicity was found. In addition, patients with active ITP were found to have cytotoxic T-lymphocytes against their own platelets. According to our data, based on the observation of 388 children with acute ITP, 92.6% of patients had an increase in the level of CD3+ T-lymphocytes and a decrease in the level of CD4+ T-lymphocytes, as well as an increase in CD19 B-lymphocytes [7.p.24.].

Suppression of immunological tolerance. The appearance of antiplatelet antibodies and antiplatelet cytotoxic T-lymphocytes is a consequence of the loss of immunological tolerance by antigens (AG). T-lymphocytes, having recognized peptides with native GPIIb/IIIa in the normal process, prevent their entry into the thymus (negative selection), since GPIIb/IIIa has been shown to be on the surface of epithelial cells and is formed from the thymus stroma at the beginning of intrauterine life. life. However, Filion et al. showed that autotoxic T-lymphocytes directed against GPIIb/IIIa are present in the peripheral blood of all healthy individuals. This means that peripheral tolerance mechanisms are critical to prevent the activation of autotoxic T-lymphocytes. In the course of studies on the mechanisms of immune defense in patients with ITP, significant points have been identified. Among them is a decrease in the number of CD4 + CD25 + normal T-lymphocytes and a violation of their suppressive activity compared with healthy subjects. In addition, CD3+ T-lymphocytes in patients with active manifestations of ITP change the expression of genes associated with apoptosis and are significantly more resistant to corticosteroid therapy compared to normal lymphocytes. Since B-lymphocytes are involved in the immune conflict, autotoxic clones are suppressed by the bone marrow. If some B-lymphocytes suppress peripheral mechanisms, then the functional balance in the inhibitory effect of Fc receptors is important, which can affect the maintenance of tolerance. The role of antigen-presenting cells (APCs) in the suppression of tolerance in ITP in model studies remains unclear, but these cells are critical in generating new, unknown epitopes from platelet glycoproteins. Expression of these new peptides by APCs, with simultaneous stimulation of the molecules, activates T-lymphocytes, which are recognized as additional platelet antigens. Thus, it allows the recognition of a new, independent determinant or epitope of distribution, which may play an important role in the activation and chronicity of ITP. Clones of T-lymphocytes that react with unknown epitopes can avoid undesirable selection in the thymus if these factors are present at subthreshold concentrations [9.p.524].

The role of intercellular interactions. Intercellular interactions are important for the activation of T-lymphocytes, B-lymphocytes and macrophages. Optimally, two pulses are required for T-cell activation. The first impulse for T-lymphocyte receptors is the formation of peptide complexes with the histocompatibility complex. The second impulse is provided by the interaction of CD28, CD2 and LFA-1 on T-lymphocytes with their cofactor ligands B7, LFA-3 and ICAM-1, respectively, on APCK. Activated T cells produce cytokines that promote B cell differentiation and AT production. Further interaction of T cells with B cells via CD154 (CD40–CD40L) is necessary to maintain platelet autoimmunization. Platelets self-express CD154. Normally, the level of CD154 on the platelet surface is low, but increases after platelet activation. An increase in the level of CD154 and its related RNA was found in platelets and megakaryocytes of patients with ITP, and they are able to control the activation of B-lymphocyte autoreactions, which suggested a possible active role of platelets in the autoimmune process. Finally, an increase in the level of CD80 (B7-1) on platelets in patients with ITP was noted, and the influence of the B7/CD28 cofactor in the pathogenesis of this disease was also shown.

Modern approaches to the therapy of patients with ITP Despite repeated randomized trials, there is still no consensus on the treatment of ITP. In addition, in some patients, adverse reactions from therapy may exceed the problems caused by ITP itself. When choosing therapy for patients with ITP, the age of the patient, the severity of the disease, and the social conditions of the patient should be taken into account. Unlike children, adult patients, especially over 60 years of age, have a higher risk of dangerous, fatal bleeding. However, specific therapy may not administered despite platelet count <20•109/l and the presence of extensive bleeding. Indeed, symptomatic therapy of patients with ITP, even those at risk of bleeding, is now increasingly used. As for acute ITP in children, in our opinion, expectant management is not justified, since this can lead to chronic ITP and the ensuing consequences. Children with severe hemorrhagic syndrome (skin hemorrhages, bleeding) and thrombocytopenia less than 50×109/l are shown to be given specific therapy. ITP therapy is divided into first and second line therapy. First line therapy. Once a decision has been made to assign a specific therapy to a patient with ITP and the patient is in a non-life-threatening condition, corticosteroids are the standard first-line drugs for him. The mechanisms of action of corticosteroids in ITP are still unclear, although they are known to reduce the destruction of platelets coated with antibodies by macrophages; reduce the production of antiplatelet antibodies, and also strengthen the vascular wall of capillaries. In practice, prednisolone per os is prescribed at a dose of 1–2 mg/kg per day, once or fractionally, taking into account the daily rhythm.

Approximately 2/3 of children on the background of corticosteroid therapy achieve a complete or partial response, and in most cases within the 1st week of treatment [6]. However, among adult patients with ITP, only 10–15% of patients treated with prednisolone maintain a stable remission of the disease in the future [40]. Two large non-randomized studies have shown that a short course of therapy with high oral doses of dexamethasone (40 mg/day for 4 consecutive days) was more effective than standard dose therapy. However, despite this effect, the use of this regimen as a first-line therapy is not currently recognized. According to our data, in children with ITP, the effectiveness of corticosteroid therapy at a dose of 2–3 mg/kg of body weight, taking into account the daily rhythm for 3 weeks, followed by gradual withdrawal or transfer to an intermittent course, averages 78%, long-term remission (more 5 years) was noted by us in 65% of patients receiving corticosteroid therapy.

IVIG therapy is recommended for patients with life-threatening bleeding and for corticoresistant patients [6]. It has been proven that the positive effect of IVIG in ITP is associated with a temporary suppression of the reticuloendothelial system, the so-called “macrophage blockade” mechanism. To enhance the immunomodulatory effect of IVIG, the presence of circulating immune complexes, which reduce the release of pro-inflammatory cytokines from monocytes, is necessary. The IVIG preparation must meet the following requirements: 1) ensuring a high level of viral safety; 2) maximally preserved natural native structure of immunoglobulins; 3) the minimum content of polymers, aggregated particles and prekallikrein activators. It is important to pay attention to excipients in an IVIG preparation: it is well known that glycine is recognized as the best and safest excipient, which not only minimizes the possibility of side effects, but also does not need to take into account the total carbohydrate load on the patient, as is the case in cases of use in as a maltose stabilizer. In addition, allergic reactions to maltose as such are known, up to the development of anaphylactoid reactions. Of the currently existing IVIG preparations, all the criteria for modern normal human immunoglobulins are met by Intratect, an immunoglobulin of the latest generation of normal human immunoglobulins, which has not only high immunobiological efficacy, but also excellent tolerability. Intratekt is the only IVIG, in the production of which for the first time an innovative, most modern protein purification technique was used - cation exchange chromatography, which allows, on the one hand, to preserve the natural native structure of immunoglobulins as much as possible, and, on the other hand, to obtain a pure IgG antibody fraction free of polymers, aggregated particles, prekallikrein activator. Intratect is available as a ready-to-use isotonic solution, does not contain sugar, contains glycine as an auxiliary stabilizer, which minimizes the possibility of side effects after drug administration.

There are several treatment regimens for IVIG. In normal practice, the standard dose is 0.8–1 g/kg per day for 1–2 days. Approximately 80% of patients treated with IVIG achieve an increase in platelet levels of more than 50×10 9/l, of which more than half of the cases achieve complete remission. The platelet count increases after the 1st day of therapy and, as a rule, reaches its maximum value during the first week after treatment. However, this effect is temporary and persists for no more than 3–4 weeks, after which the platelet count may decrease to its original level. According to our data, the effectiveness of IVIG therapy is 63%, we noted long-term remission in 48% of children with ITP. Thus, IVIG therapy is ideal in case of need for a rapid increase in platelet levels (with life-threatening bleeding), and can also be used in combination with corticosteroid therapy. Platelet levels can be increased by using anti-D Ig, which is effective in Rh-positive non-splenectomy patients [4.p.103]. Anti-D Ig blocks D-AG of erythrocytes. According to data published to date, the effectiveness of an intravenous course of anti-D Ig in adult patients with ITP at a dose of 50 μg/kg is 70%. An increase in platelet levels was observed after 72 hours from the start of therapy and persisted for more than 21 days in 50% of those who responded to treatment. Increasing the dose of anti-D Ig to 75 μg/kg has been shown to not only increase platelet counts faster compared to the standard dose of 50 μg/kg, but also to maintain the effect of therapy longer. In addition, compared with the response within the first day from the start of treatment, the use of anti-D Ig is much more effective than the use of corticosteroids and is almost similar in terms of the effectiveness of IVIG. In several patients with chronic ITP, antiD was administered subcutaneously. None of the patients with this method of administration of the drug had hemolytic or any other complications. In addition, the effectiveness of this method of administration, as it turned out, is similar to that observed with intravenous administration.

III. CONCLUSION

Despite the fact that the basic principles of the pathophysiology of ITP have been known for more than half a century, important new discoveries have been made relatively recently. The concepts of the pathogenesis of the development of thrombocytopenia have moved from traditional views that thrombocytopenia is caused by the production of auto-AT to platelets, leading to their destruction, to more complex mechanisms in which a violation of platelet production and their destruction is also associated with T-cell mediated effects. And these processes, as it turned out, are no less important and play a significant role in the pathophysiology of thrombocytopenia. In addition, new approaches to therapy, such as the use of Rituximab in adult patients with ITP, have shown their effectiveness.

These data are especially important for those patients who need to delay or avoid splenectomy. Thrombopoiesis factors (AMG531, Eltrombopag) can become a breakthrough in the treatment of ITP, including refractory forms of the disease, due to their high efficacy, shown in the course of studies.

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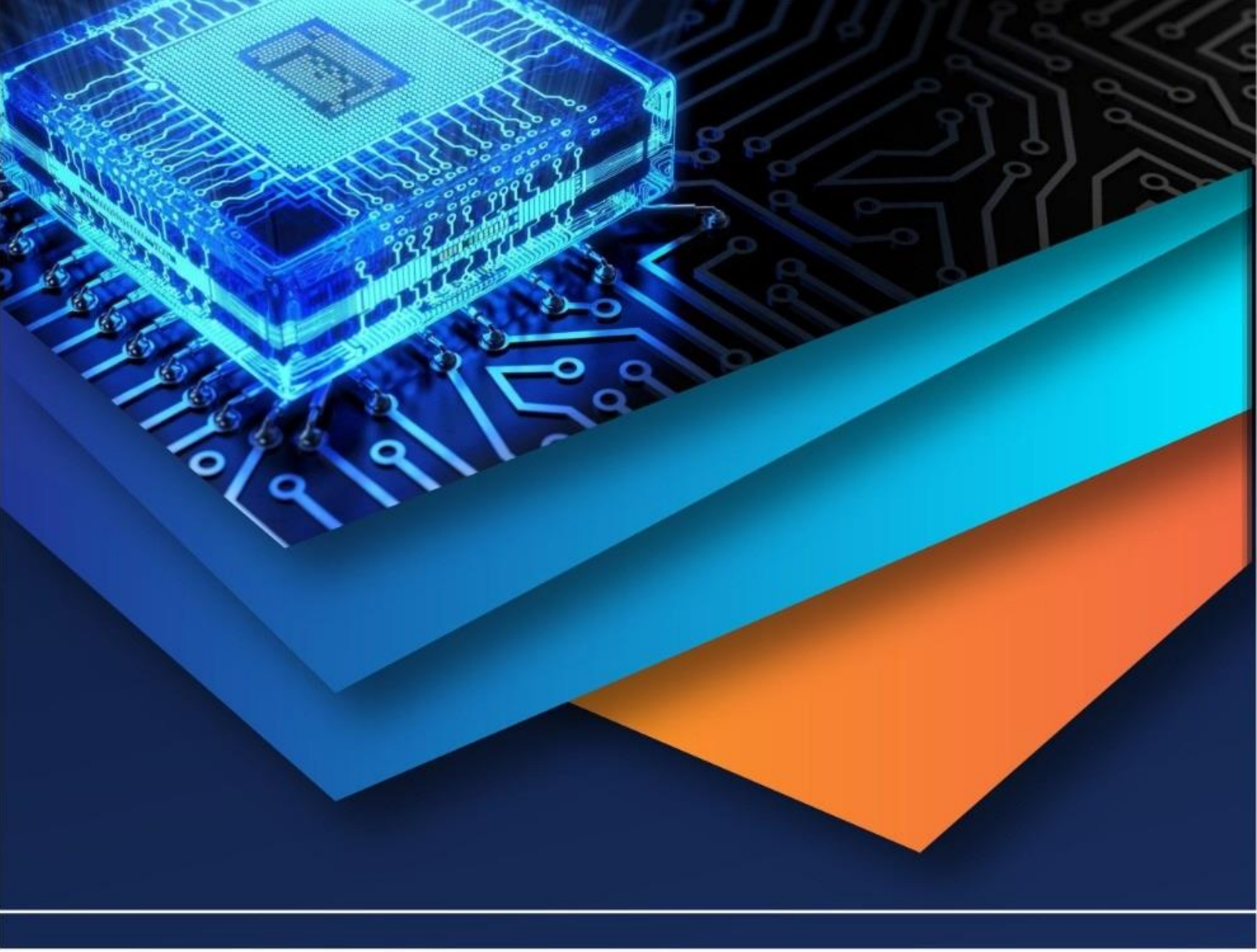

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