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# Pathogenetic justification for the therapy of idiopathic thrombocytopenic purpura (primary immune thrombocytopenia) in adults

*I.I. Zotova, S.V. Gritsaev*

*Russian Scientific Research Institute of Hematology and Blood Transfusion of the Federal Medical-Biological Agency, Saint Petersburg, Russia*

## Abstract

The review presents current data on key mechanisms of the pathogenesis of idiopathic thrombocytopenic purpura and comparative characteristics of main therapy methods. In recent years, the interest in studying this long known disease has significantly increased, and basic approaches to diagnosis and treatment have been revised. Recognition of the importance of immune-mediated mechanism of development of this disease led to the replacement of the term used for many years «idiopathic thrombocytopenic purpura» to «immune thrombocytopenia». Moreover, development of hemorrhagic manifestations (purpura) is known to be characteristic not for all patients. The basis for the disease development is imbalance between the process of platelet production and destruction, as reflected in decrease of platelet production and increase of their elimination. Conventional treatment methods such as corticosteroids and splenectomy are directed at the suppression of a complex of cell interactions that lead to increased platelet destruction. Modern therapy for idiopathic thrombocytopenic purpura — thrombopoietin receptor agonists, on the contrary, stimulate the platelet production and are recommended for the use when loss or lack of response to previous therapy are observed. Most likely the efficacy of these drugs in resistant idiopathic thrombocytopenic purpura is associated with a fundamentally different, alternative mechanism of action. The idiopathic thrombocytopenic purpura group of patients is heterogeneous both in the character of the disease course and possible response to treatment. A limited number of clinical trials of some treatment methods for idiopathic thrombocytopenic purpura and differing criteria for assessing the response to therapy complicate their direct comparison. The imperfection of certain treatment options, due to development of adverse events, and unpredictability of response to treatment necessitate the search for new approaches to the selection of the optimal variant of treatment of idiopathic thrombocytopenic purpura taking into account the individual characteristics of patients.

**Keywords**: immune thrombocytopenia, megakaryocytopoiesis, thrombopoietin, line of therapy.

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Idiopathic thrombocytopenic purpura (ITP), or primary immune thrombocytopenia, is an acquired autoimmune disease that occurs in children and adults and is characterized by an isolated reduction in the number of platelets $<100 \times 10^9$/L in the peripheral blood in the absence of other causes or diseases that could cause thrombocytopenia [1–6]. The recent research on the pathogenesis of ITP reveals that its development is based on the increased destruction of platelets by macrophages because of the synthesis of autoantibodies to the structures of the platelet membrane and megakaryocytes (MKC) and inadequate megakaryocytopoiesis in the bone marrow [7–11]. In patients with ITP, platelets are associated with antibodies represented by class G immunoglobulins that identify glycoproteins GpIIb/IIIa and GpIb/IX located on the membranes of platelets and MKCs, which disrupt the platelet maturation and release [12]. Occasionally, antibodies of multiple specificities are directed against other antigens of the platelet surface [13, 14].

For several years, the synthesis of anti-GpIIb/IIIa antibodies with B-lymphocytes and plasma cells was considered to be the only pathophysiological mechanism of the ITP development. However, recent research has revealed that the pathology of the T-cell link of immunity plays a vital role in the pathogenesis of ITP. Reportedly, B-lymphocytes require the presence of specific $CD4^+$ T cells [T helpers (Th) and regulatory T cells (Tregs)] to generate antibodies against normal platelet antigens [9, 10]. The primary function of the latter is to prevent autoimmune diseases.

Suppression of the immune response is provided by a mechanism based on a three-way interaction between Tregs, Th, and antigen-presenting cells. Moreover, the ability of Tregs to suppress B cells independently has

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been established previously [11], ensuring the ability of Tregs to prevent the development of autoimmune diseases, including primary ITP. In addition, an upsurge in the number of $CD8^+$ T-lymphocytes exerting a cytotoxic effect on platelets and MKC and $CD3^+$ T-lymphocytes involved in cell-mediated cytotoxicity through the secretion of certain cytokines inducing apoptosis of MKCs is observed in patients with ITP.

The primary manifestation of ITP is hemorrhagic syndrome (HS) of varying severity, from the absence of symptoms of bleeding or minimal manifestations on the skin and mucous membranes to severe, life-threatening bleeding. Uterine, gastrointestinal hemorrhages, and hematuria are rare, long with subarachnoid hemorrhages, the incidence of which does not exceed 0.5% and is mostly reported in therapy-resistant and elderly patients with concomitant diseases [7, 15, 16]. The annual risk of bleeding with a fatal outcome in patients with ITP is approximately 1.6%–3.9% [17]. Manifestations of HS depend on the level of thrombocytopenia. Apparently, with a platelet count $>30–50 \times 10^9$/L, spontaneous HS rarely appears, whereas a prolonged reduction in the number of platelets $<30 \times 10^9$/L is a risk factor for clinically significant bleeding [4, 7, 16].

Patients with ITP represent an extremely heterogeneous group. Several patients with ITP, even with very low platelet counts, exhibit no manifestations related to thrombocytopenia, whereas others might develop bleeding of varying severity from the onset of the disease. Thus, Rodeghiero et al. followed up patients with ITP in the routine clinical practice for >12 months and reported that 40%, despite the low platelet counts, experienced no bleeding and did not require treatment [18]. Severe ITP, resistant to conventional therapeutic methods, develops in 8%–10% of patients [19]; this group of patients exhibit higher mortality rates for 5 years (47.8%) and risk of significant bleeding at a 2-year follow-up (76%) [17].

Of note, data on the incidence and prevalence of primary ITP are rather limited. The incidence ranges 1.6–3.9 new cases per 100,000 people per year. In addition, the prevalence rates vary considerably in different studies (from 4.5 to 20 per 100,000 population) [16, 20]. In the Russian Federation, information available on the epidemiological and demographic characteristics, as well as the specific characteristics of the disease course, efficiency, and safety of various therapies are inadequate. Hence, certain achievements of the joint work of Russian hematologists are traced in recent years on the way to solving this socially significant problem; this is confirmed by studies comprising the interim analysis of the data of the Russian registry of patients with primary ITP [16, 21], as well as their presentation at the Congress of the European Society of Hematologists in 2017. The information obtained with the use of the register offers data not only about the incidence and prevalence of ITP but also about therapeutic methods used in various regions of the country. Given the need for long-term and expensive treatment for some patients with ITP, the data provided by the registry could further facilitate a comprehensive pharmacoeconomic analysis of several treatment programs and optimize the expense of the healthcare budget while maintaining a high level of medical care.

Patients with IPT represent a heterogeneous group not only in clinical manifestations but also in the possible response to treatment. This therapy aims to prevent the risk of hemorrhagic complications by increasing the number of platelets to a safe level, ensuring patients' normal existence and not reducing their quality of life. Most guidelines recommend starting treatment with a reduction in the number of platelets to $\leq 30 \times 10^9$/L because of an increased risk of bleeding, primarily intracranial [2, 20].

As the disease occurs with insignificant manifestations of HS in some patients, there is a tendency to use minimally toxic methods of treatment, which is primarily crucial for prolonged therapy of patients with a refractory or recurrent course of the disease. In addition, in several patients, treatment-related adverse events (AEs) might be more significant than disease-related problems [22]. Thus, the definition of treatment tactics and the selection of the therapeutic method in ITP are based on an individual approach, conditioned not only by the number of platelets but also by the severity of HS, comorbidity, patients' way of life, complications from previous treatment, and planned invasive interventions [2–4, 6].

Previously, a group of international and Russian experts in the field of ITP developed recommendations for treatment based on the existing literature and clinical research data [2, 4–6]. The selection of first-line drugs has remained unchanged over the past decades and includes glucocorticoids (GCs), intravenous immunoglobulin, and anti-D immunoglobulin (anti-D) in countries where the latter is registered for use. GCs are a cheap and fast method of treating ITP. With the prednisolone therapy in a standard dose of 1 mg/kg,

the platelet count increases within 1–2 days in 75% of patients; however, in most cases, the response to therapy remains unstable. Relapse after the cessation of treatment is a common occurrence, and the likelihood of its development cannot be predicted. Several studies have provided data on the frequency of remissions. Thus, based on the findings of Cuker et al., approximately 40%–60% of patients support the response within 6 months, whereas 20%–30% of patients support it within 1–2 years [23]. Reportedly, AEs of GCs are extensive and predictable, which limits their long-term use in most cases [2, 4, 6, 13].

Therapy with intravenous immunoglobulin is recommended for GC-resistant patients, or in the presence of contraindications to GC treatment, in case of the risk of severe bleeding. An elevation in the number of platelets $>50 \times 10^9$/L reaches approximately in 80% of patients after the first day of therapy with intravenous immunoglobulin. As a rule, it attains its maximum value at the end of the first week after the treatment completion [24]. However, this effect is temporary and lasts no longer than 3–4 weeks, after which the number of platelets might decline to the initial level [3]. The primary indications for the use of intravenous immunoglobulin in ITP are urgent situations in which rapid growth in the number of platelets is necessary, for example, in the case of profuse bleeding or preparation for urgent surgical interventions [2, 4, 6].

In the case of a continuously recurring ITP that warrants constant therapy to sustain a safe level of platelets, a second-line therapy is suggested. The treatment options could be classified into two groups as follows: (a) one-time or one-course with the expected development of long-term remission [splenectomy (SE), rituximab] and (b) requiring continuous or chronic administration [repeated prescription of GCs, thrombopoietin receptor agonists (TRAs), immunosuppressants] [1, 2, 4].

SE has been used in ITP for over the past 100 years and is recommended in case of the loss of response to initial therapy [2, 4–6, 25]. In various studies, the frequency of response to SE is up to 80%. Kojouri et al. reported that a steady increase in the platelet count to $150 \times 10^9$/L was observed in 66% of patients for 5 years after SE with an average follow-up period of 28 months [26]. In addition, approximately 14% of patients do not respond to SE, and relapse occurs later in 20% of those who respond [27]. Najean et al. reported that the majority of ITP relapses after SE occur within the first 2 years after surgery [28]. Some patients who did not reach remission in the immediate post-SE period later exhibit partial response with a platelet level higher than that before surgery [29]. The frequency of complications from SE is extensive and depends on several factors [22, 25, 26, 30]. SE is related to postoperative complications, such as bleeding and thrombosis, as well as a high risk of developing severe bacterial infections with the need for prophylactic vaccination and revaccination, which accounts for additional inconveniences and decreases the quality of life of patients [18].

Often, the second-line therapy is an attempt of repeated prescription of GCs. Hence, the findings reported by a group of Turkish researchers on the review of treatment results of patients with ITP in the case of the failure of the first-line therapy are exciting. Within the framework of the study, a comparative analysis of the response to therapy was performed for the repeated prescription of GCs and SE as the second-line option. The complete response was attained in 44% of patients who received GCs and 68% who underwent SE. The Kaplan–Meier curves revealed that the duration of the response obtained after SE was considerably higher than the repeated use of GCs. The long-term relapse-free survival rates in patients using GCs and SE were 13% and 58%, respectively. Thus, SE was, seemingly, the most effective in patients not responding to GCs in the first-line therapy [31]. If the repeated prescription of GCs or SE is ineffective, and if there are contraindications to surgical intervention, or patient's refusal to undergo surgery, an immunosuppressive therapy, including monoclonal anti-CD20 antibody rituximab, is possible [2, 7].

According to the national clinical guidelines, no registration of rituximab exists currently as a drug approved for the treatment of patients with ITP [6]. However, its use is possible by the decision of the medical commission in the presence of life-saving indications and a patient's consent. Notably, despite extensive use in the clinical practice, the efficacy and safety of rituximab in ITP awaits confirmation by data from well-planned, multicenter, randomized clinical trials. Given the ongoing study of the use of the drug in patients with ITP, the literature data on the outcome of treatment remains debatable [32, 33].

Attaining the response to therapy in some patients is feasible with the use of other immunosuppressive drugs (such as azathioprine, danazol, dapsone, cyclosporin A, and cyclo-

phosphamide). However, their average efficacy in ITP does not exceed 30%–35% [2–4, 6]. Furthermore, the response to therapy is typically unstable, and the treatment is accompanied by the development of a considerable amount of AEs, which limits the use of these drugs, especially in the chronic form of the disease [3]. Thus, the methods of drug therapy of ITP in the second and more lines do not enable attaining the relapse-free disease in most patients. Besides, unacceptable treatment-related AEs and the high cost of certain drugs hinder their prolonged application [2].

The issues about the search of selection criteria and justification of the application of the certain therapeutic methods at the inefficiency of the previous treatment in some patients still holds relevance; this involves the development of an algorithm of therapy in separate stages, which should be based on the principle of scientifically grounded choice. The action of first-line therapeutic drugs aimed at decreasing the destruction of platelets and restoring the standard immune response by reducing the interaction between the platelet antigen and antigen-presenting cells. In addition, the drugs act on B and plasma cells, thereby decreasing the synthesis of autoantibodies and normalizing the impaired functions of Tregs. Likewise, the second-line therapeutic methods result in the normalization of the immune response by increasing the number of Tregs. In the case of the development of the refractory course of ITP, a combination of several therapeutic approaches is required in some patients to ensure the restoration of the physiological amount of platelets [15]. Thus, considering the clinical variability of patients with ITP, as well as the involvement of various mechanisms in the development of the disease, only a comprehensive approach to investigate the characteristics of the disease course and possible response to ongoing therapy could help elucidate the unique aspects of ITP and provide a theoretical basis for further research on the efficacy of various therapies. The search for a possible correlation between the characteristics of the immune response and the development of refractory or relapsing forms of ITP, which are the most difficult when selecting a therapeutic method, becomes highly relevant.

In recent years, TRAs have been successfully used to treat patients with ITP, with their action based on the mechanism of stimulation of megakaryocytopoiesis by acting on thrombopoietin receptors [2, 7, 8, 16, 34]. The drugs interact directly with MKCs, stimulating the production of platelets, and exert an indirect immunomodulatory effect on Tregs. The diversity and multiplicity of the receptors of megakaryocytic cells suggest the presence of various regulators of megakaryocytopoiesis and thrombocytopoiesis. Thrombopoietin or c-mpl ligand (megakaryocytic growth and differentiation factor) is the primary cytokine that exerts a specific effect on the megakaryocytic line, beginning with the early precursors of megakaryocytopoiesis [35]. The major mechanism of maturation of MKC and platelet production is an interaction between thrombopoietin and the mpl receptor. In the receptor, cytoplasmic, transmembrane, and extracellular domains are isolated.

The absence of a compensatory increase in the thrombopoietin level in response to pronounced immunomediated thrombocytopenia is one of the principal pathophysiological mechanisms of the ITP development [8, 13, 34, 35].

Comprehending the role of the impaired platelet production in the ITP pathogenesis accounted for developing biotechnological products capable of stimulating the thrombopoietin receptor and enhancing the platelet formation. Consequently, TRAs appeared to be capable of simulating the effect of endogenous thrombopoietin [36]. Over the past 10–15 years, several randomized clinical trials have assessed the efficacy and safety of the TRAs use in ITP to investigate the duration of treatment and the ability to maintain the platelet level in the event of the futility of previous therapy. The findings of the studies were crucial for the registration of romiplostim and eltrombopag in several countries of the world, including Russia.

Of note, both drugs are TRAs and differ in the region of interaction with the receptor; while romiplostim binds to the extracellular domain, eltrombopag binds to the transmembrane part of the receptor. Furthermore, differences exist in their administration route; while eltrombopag is prescribed orally, romiplostim is administered subcutaneously. Attaining platelet response is observed in 79%–88% of patients with the application of romiplostim and 79% of patients receiving eltrombopag. Both drugs are effective irrespective of the initial level of platelets, prior therapy, and the SE status, which has been demonstrated both for romiplostim [4, 37] and eltrombopag [38]. The use of TRAs facilitated in the reduction of the frequency of severe bleeding and the need for urgent measures. Another distinctive feature was the acceptable safety profile, and the

absence of an elevation in the number of AEs as the duration of therapy was increased. In addition, along with therapy with TRAs, other treatments of ITP were possible to discontinue in some patients (for example, long-term therapy with GCs) [39]. Furthermore, the results of comparative studies of the efficacy of TRAs with other therapy variants of ITP are of undoubted practical interest. Thus, in particular, Wasser et al. reported a higher efficacy of romiplostim compared with rituximab in unsplenectomized patients with chronic ITP in the second-line therapy [40].

Any new therapeutic approach in patients with ITP aims at the safety of therapy and the stability of platelet response in the long-term use. In recent years, the studies of TRAs have been directed toward the investigation of the long-term efficacy and safety of long-term continuous therapy, including the likelihood of developing AEs such as the deposition of reticulin and collagen fibers in the bone marrow [41, 42] and thrombotic complications [38, 39, 43]. In addition, recent reports on the possibility of long-term maintenance of persistent platelet response (remission) in some patients with resistant ITP after the discontinuation of treatment using TRAs are of considerable interest. Apparently, after the cessation of therapy with TRAs, the number of platelets typically decreases to the initial value after 2–3 weeks. However, in some cases, the platelet count might be maintained at a level sufficient to maintain hemostasis after the discontinuation of therapy in the absence of another treatment of ITP [44, 45].

In recent years, the likelihood of the direction of clinical trials to investigate the efficacy of TRAs is also oriented toward considering the possibilities of earlier prescription of drugs. Thus, for the first time, Newland et al. (2016) assessed the frequency of attaining remission in the treatment with romiplostim in patients at the early stages of ITP (≤6 months from establishing the diagnosis). They attained platelet response in 93% of patients and noted the development of remission in 32% of patients who received romiplostim during ≤12 months. Thus, the early discontinuation of romiplostim might be possible for patients not only with chronic ITP, as reported in previous studies, but also the persistent stage of the disease. In addition, the study demonstrated that a higher amount of platelets was associated with the development of remission during the first 2 months of therapy, whereas in patients who did not achieve remission, a lower value of the indicator in this period was noted [46].

Despite the fact that the involvement of the immune system in the formation of ITP has been established for a long time, no less critical discoveries continue to occur in our days. The agonists of the TRA receptor, which demonstrated the efficacy and safety in the course of the studies, and rapidly entered into the usual clinical practice, undoubtedly became the discovery of the last decade. Meanwhile, many unresolved issues remain both in the selection of therapeutic methods of ITP and in the study of the clinical and biological heterogeneity of patients. When reviewing foreign and Russian publications, a heterogeneous picture can be traced from the results of ITP therapy both in general and based on the use of TRAs in particular [47–49]. The opposing groups of patients with ITP, such as those refractory to therapy and maintaining a lasting, sustained response after the withdrawal of treatment, remain partially investigated.

Overall, additional studies to identify markers of the prognosis of the severity of the disease course and the response to therapy, followed by the isolation of various groups of ITP patients, are highly warranted.

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