Research Results in Pharmacology

Research Results in Pharmacology 9(1): 49–59
UDC: 616.155.294-053.2+615.015
DOI 10.18413/rrpharmacology.9.10011

Review Article

Thrombopoietin receptor agonists in pharmacotherapy of pediatric immune thrombocytopenia

Olga S. Levchenkova[1], Viktoriya V. Vorobieva[2], Vasiliy E. Novikov[1], Tatiana I. Legonkova[1], Elena N. Volkova[3]

1 *Smolensk State Medical University, 28 Krupskaya St., Smolensk 214019 Russia*
2 *Kirov Military Medical Academy, 6-Zh Academician Lebedev St., St.-Petersburg 194044 Russia*
3 *Voronezh State Medical University named after N.N. Burdenko, 10 Studencheskaya St., Voronezh 394036 Russia*

Corresponding author: Olga S. Levchenkova (os.levchenkova@gmail.com)

Academic editor: Tatyana Pokrovskaia ♦ **Received** 05 December 2022 ♦ **Accepted** 06 March 2023 ♦ **Published** 31 March 2023

Citation: Levchenkova OS, Vorobieva VV, Novikov VE, Legonkova TI, Volkova EN (2023) Thrombopoietin receptor agonists in pharmacotherapy of pediatric immune thrombocytopenia. Research Results in Pharmacology 9(1): 49–59. https://doi.org/10.18413/rrpharmacology.9.10011

Abstract

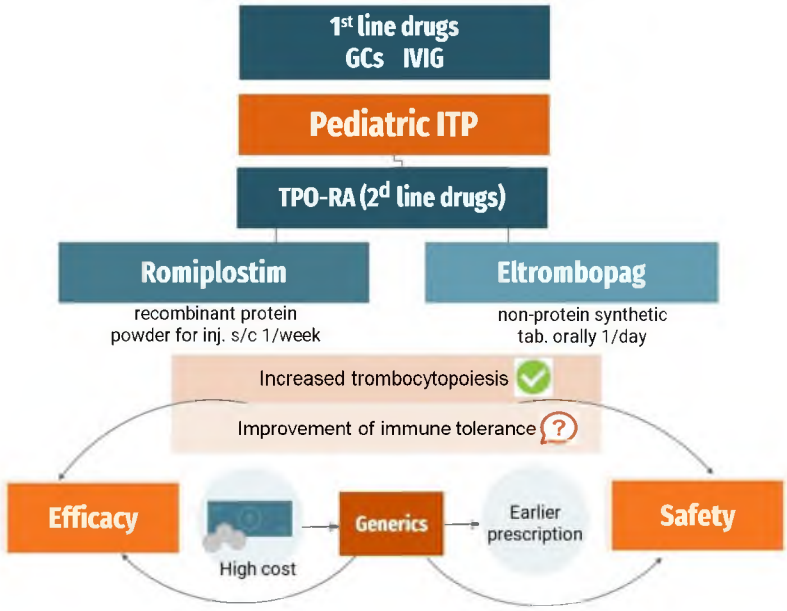
Introduction: Thrombopoietin receptor agonists are commonly second-line drugs in immune thrombocytopenia (ITP) pharmacotherapy in children and prescribed for chronic ITP refractory to first-line therapy.

Standard ITP pharmacotherapy in children: includes prescribing glucocorticoids or intravenous immunoglobulins.

Thrombopoietin receptor agonists: Currently Romiplostim and Eltrombopag are used in the Russian Federation pediatrics. Their pharmacodynamic features in comparison with other drugs used in ITP are presented in the paper. Increased thrombocytopoiesis is the dominant, but not the only component of Romiplostim and Eltrombopag mechanism of action. It is relevant to study their effect on immune tolerance in ITP, which may be associated with a persistent platelet response in some patients after drug discontinuation.

Conclusion: The issue of thrombopoietin receptor agonist efficacy and safety as well as the mode of their use in ITP children treatment continues to be studied. The high cost of drugs continues to be a limiting factor to their earlier prescription. Generic drugs – Romiplostim and Eltrombopag partly solve the problem, promote their earlier prescription in ITP, but require additional study of their bioequivalence and therapeutic equivalence in comparison with the original drugs.

Graphical Abstract



Keywords

immune thrombocytopenia, thrombopoietin receptor agonists, Romiplostim, Eltrombopag.

Introduction

Immune thrombocytopenia (ITP), until 2009 called idiopathic thrombocytopenic purpura, is a rare disease characterized by isolated immune-mediated thrombocytopenia (platelet count less than 100×10^9/L) with or without hemorrhagic syndrome of varying severity. A decrease in the platelet number occurs due to their autoimmune destruction, as well as impaired proliferation of megakaryocytes and the formation of platelets from them (Krysanov et al. 2017; Zotova and Sergeev 2018; Vishnu and Aboulafia 2020). Up to 10% of patients with ITP suffer from major bleeding, including 0.1% to 0.9% of cases with life-threatening intracranial hemorrhages (Nolla et al. 2020). The incidence of ITP in the world is 1.6–3.9 per 100,000 adults per year, in children – from 1.9 to 6.4 per 100,000 (Payandeh et al. 2018), which makes it possible to classify as a rare (orphan) disease (Krysanov et al. 2017). At the same time, newly diagnosed acute ITP (up to 3 months from the moment of diagnosis) in 30% of cases turns into persistent (prolonged, lasting 3-12 months), and in 5-10% into chronic (lasting more than 12 months) (Zotova et al. 2017).

The main mechanism for the ITP development is an intensive platelet destruction by macrophages as a result of specific autoantibodies to platelet membrane receptors (recognition is carried out by glycoproteins GP IIb/IIIa and GP Ib/IX) and megakaryocytes (MKC), which subsequently disturbs megakaryocytopoiesis (Zotova et al. 2017; Kontievsky and Golenkov 2019; Singh et al. 2021). The platelet destruction is caused by the binding of sensitized platelets to the Fc receptors (FcyRIIA and FcyRIIIA) of phagocytes, followed by their uptake by spleen macrophages (less often by liver and lymph node macrophages), as well as platelet destruction by complement-mediated lysis, especially in the presence of anti-GPIb /IX antibodies (Rumyancev and Maschan 2015).

Disbalance of T helper cells (Th1/Th2), which leads to an increase in the number and activity of cytotoxic T cells, plays an important role in ITP pathogenesis. An increased number of cytotoxic CD8+ and CD3+ T-lymphocytes inhibits platelet activity and induces their apoptosis through cell-mediated reactions (Zotova et al. 2017; Zotova and Sergeev 2018). In addition, a potent decrease in the activity of regulatory T-cells (Tregs) leads to dysregulation of T-helper-mediated B-cell activation. B cells produce a lot of autoantibodies, resulting in opsonization, phagocytosis, complement activation and platelet destruction. Both the variant with enhanced peripheral clearance of platelets, and, on the contrary, the variant with a marked reduced platelet formation with a mild reduced platelet life can dominant in the thrombocytopenia mechanism (Rumyancev and Maschan 2015).

Due to autoimmune nature of the disease, the standard ITP pharmacotherapy includes immunosuppressive drugs (glucocorticoids,

immunosuppressants, monoclonal antibodies) and immunomodulatory drugs (immunoglobulin drugs). However, their use does not always produce the desired effect. In recent years, thrombopoietin drugs and thrombopoietin receptor agonists have been used in the ITP treatment. Their pharmacodynamics, drug regimens and place in the ITP pharmacotherapy are currently being actively studied.

The aim of the research is to analyze the results of modern scientific studies of the efficacy and safety of thrombopoietin receptor agonists for the ITP treatment in children in comparison with standard pharmacotherapy.

Standard ITP pharmacotherapy in children

Currently, newly diagnosed pediatric ITP without severe hemorrhagic syndrome, due to the possibility of spontaneous remission during the first 2 months, are advised to be managed with observation tactics "watch and wait" (Petrov 2016; Cooper and Cines 2019; Neunert et al. 2019; Suntsova et al. 2020). The specific pharmacotherapy, first of all, is indicated for those patients who have a marked hemorrhagic syndrome and thrombocytopenia less than 20-30×10^9/L (Rumyancev and Maschan 2015; Petrov 2016; Suntsova et al. 2020).

The standard first-line drugs for newly diagnosed ITP treatment are glucocorticoids (GC) and intravenous immunoglobulins (IVIG) (Petrov 2016; Zotova et al. 2017; Suntsova et al. 2020; Yasser et al. 2020). First-line therapy for chronic ITP (cITP) treatment includes IVIG or anti-Rh-D immunoglobulin, second-line therapy includes GCs (Prednisolone, Dexamethasone, Methylprednisolone), immunosuppressants (Mycophenolate mofetil, Azathioprine, Cyclosporine, Cyclophosphamide, Vinblastine, etc.), monoclonal antibody drug Rituximab (Giordano et al. 2020; Miltiadous et al. 2020; Yasser et al. 2020; Park et al. 2022). The pharmacodynamic sign of the therapy effectiveness is the platelet response, which in turn is divided into persistent – achieving a constant platelet count above 50×10^9/L without bleeding and/or the need for emergency therapy and short-term – a single increase in platelet number more than 50×10^9/L during end period of time.

Glucocorticoids (GCs) have been used quite effectively in ITP pharmacotherapy for many decades (Bredlau et al. 2011, Neunert et al. 2019, Warrier and Chauhan 2012). In Russia, GCs are still often chosen as the primary treatment for ITP patients. GCs inhibit a complex of cellular interactions that lead to increased destruction of platelets in ITP (Zotova et al. 2017). In the GC mechanism of action in ITP, it is known that they reduce the production of antiplatelet antibodies and the vascular wall permeability (Shabanov and Vorobieva 2020). GCs have a wide range of effects on immune cells (macrophages, T and B cells), Fc receptors, reducing platelet destruction. Approximately 70% of patients with GC therapy achieve a complete or partial platelet response in most cases during the first week of treatment (Petrov 2016), but often the response to therapy is unstable (Zotova et al. 2018).

Intravenous immunoglobulins (IVIG) are polyspecific IgG drugs, the mechanism of action of which is associated with an increase in the functional activity of Tregs and blockade of macrophage Fc receptors, which reduces the platelet opsonization by autoantibodies and prevents their destruction by spleen macrophages (Petrov 2016). Besides, IVIG can block neonatal Fc receptors on the endotheliocyte surface and accelerate antiplatelet antibody catabolism (Shabanov and Vorobyova 2020). IVIG has been used for about 30 years in the ITP treatment, being currently the drugs of choice, especially if it is necessary to achieve a rapid effect (the effect develops after 24-48 hrs, which is faster compared to GCs).

Based on the literature data, approximately 70-80% of patients after using IVIG for 2-5 days have an increase in platelet count up to more than 50×10^9/L, a complete remission occurs in half of the cases (Singh et al. 2021). By the end of the first week of IVIG therapy, the platelet count reaches its maximum values; however, this is often temporary and persists only for 3-4 weeks, after which it may decrease to the initial level (Petrov 2016). The use of IVIG requires a long (5-8 hrs) infusion. Side effects of IVIG are headache, fever, nausea, vomiting, rarely aseptic meningitis, acute renal failure, very rarely – acute intravascular hemolysis (Bredlau et al. 2011; Rumyancev and Maschan 2015; Petrov 2016; Singh et al. 2021).

The combined use of GCs and IVIG is possible, especially for bleeding from the mucous membranes, extensive petechiae, purpura and ecchymosis, symptoms of internal bleeding. The use of these drugs leads to a more rapid increase in the platelet count due to synergistic interaction (Petrov 2016).

Anti-Rho(D)-immunoglobulin (Anti-D) also belongs to the first-line ITP pharmacotherapy. Anti-D can be prescribed only for RhD-positive children in acute and chronic ITP with a sufficient hemoglobin level who have not undergone splenectomy (Williams 2016). The mechanism of Anti-D action is associated with the blockade of Fc receptors of spleen macrophages, which disturbs platelet phagocytosis. Anti-D is injected much faster (within 10-15 min) compared to slow IVIG infusions. An increase in platelet levels occurs within 1-2 days, reaching a peak by 7-14 days. Side effects are fever, nausea, and mild hemolysis. Since 2010, due to information about the potential risk of severe hemolysis, Anti-D-induced disseminated intravascular coagulation, it has been prescribed much less frequently (Long et al. 2012). Anti-D is not used for the treatment of ITP in Russia.

Second-line drugs used for ITP include **immunosuppressants,** such as Azathioprine, Cyclosporine, Cyclophosphamide, Vincristine, Mycophenolate mofetil, etc., for which ITP is an off-label use. Their mechanism of action is associated with T- and B-cell inhibition. The choice is determined by the doctor experience of their use, since the most important principle of ITP treatment is its individualization, and the clinical and laboratory response to immunosuppressants is unstable in most cases (Rumyancev and Maschan 2015; Gudbrandsdottir et al. 2020; Yasser et al. 2020).

Rituximab (anti-CD20 monoclonal antibody) is currently available for ITP treatment. Rituximab depletes CD20+ B cells and directly reduces antiplatelet antibody production (Singh et al. 2021). It reduces the number of B-lymphocytes and antibodies, the expression of CD40 and CD80 on B-lymphocytes, which inhibits the activation of cytotoxic T-lymphocytes. Rituximab is included in second-line ITP pharmacotherapy (Fig. 1). It contributes to the stable platelet response in 40-60%, and in 30-60% – to a long-term remission (Rumyancev and Maschan 2015). The combined use of Rituximab with GC high doses (more often Dexamethasone) is possible to increase the therapy effectiveness (Zotova et al. 2017). Lack of response to Rituximab is associated with aberrant oligo-/monoclonal expansion of the T-cell mediated immune response (Vianelli et al. 2022). A meta-analysis comparing Rituximab with thrombopoietin receptor agonists used in pediatric ITP found differences in favor of the latter in terms of sustained platelet response and need for emergency surgery, as well as adverse effects (Ayad et al. 2022). There are investigations demonstrating that Rituximab role and immunosuppressants as Cyclosporine, Vincristine place in ITP treatment is rather overestimated (González-López et al. 2022). Adverse effects of Rituximab include an increased susceptibility to mild infections and, rarely, progressive multifocal leukoencephalopathy (Singh et al. 2021).

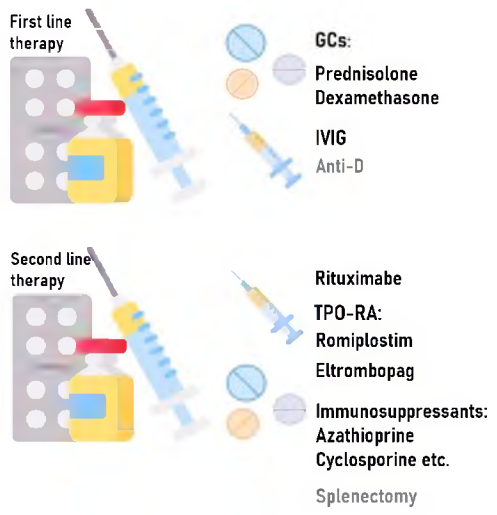


Figure 1. First- and second-line drugs used for ITP treatment in children.

Minimizing the number of drugs and applying an individual approach to each child are the most important principles of ITP treatment. The goal of treatment is not so much to stabilize the platelet count and maintain it at any normative level, but to prevent the bleeding development and stop the developed bleeding. Insufficient predictable response to ITP pharmacotherapy, both first- and second-line, the high incidence of adverse effects justifies the need to search for new approaches and drugs for the ITP treatment in children (Zotova et al. 2017).

Thrombopoietin receptor agonists

Relatively recently, thrombopoietin receptor agonists (TPO-RA) have begun to be used for ITP treatment in children. Thrombopoietin (TPO) is a protein involved in thrombocytopoiesis, the main regulator of new platelet production from megakaryocytes (MKC), and MKC maturation. It is a glycoprotein hormone synthesized by the liver, kidneys and skeletal muscles. The reduced TPO level is determined in the blood of ITP patients. Therefore, it has been suggested that activation of c-MPL thrombopoietin receptors may lead to thrombocytopoiesis normalization (Rumyancev and Maschan 2015). The hypothesis was confirmed: the use of first-generation of TPO-RA (recombinant human thrombopoietin and MKC growth factor) led to a significant increase in platelet levels, both in healthy volunteers and in patients. However, it was found that their use can activate the production of autoantibodies to TPO, which worsens the disease, so further research was terminated (Zotova et al. 2017). As TPO mimetics were based on native endogenous human TPO, anti-drug antibodies cross-reacted with natural TPO, resulting in severe thrombocytopenia.

The second generation of TPO-RA in the form of a recombinant protein (AMG351 – Romiplostim, binding to the extracellular domain of the receptor) and a small molecular weight synthetic non-protein TPO receptor agonist (SB-497115 – Eltrombopag, binding to the transmembrane part of the receptor) proved to be effective in the ITP treatment. At the same time, the risk of autoantibody formation to endogenous TPO during their use is minimal. In 2010, these drugs were registered in Russia (Zotova et al. 2017). There are currently five second-generation TPO receptor agonist drugs: the peptide Romiplostim and the low molecular weight Eltrombopag, Avatrombopag, Lusutrombopag and Getrombopag. Two of them – Romiplostim and Eltrombopag – have been prescribed for ITP treatment in children.

Romiplostim is a TPO-R peptide agonist approved more than ten years ago for the ITP treatment of adults, and since 2018, it has been used in the Russian Federation for the ITP treatment in children aged

1 year and older who have no an adequate response to GCs, IVIG or splenectomy, and whose ITP lasted more than 6 months (Al-Samkari et al. 2020).

Romiplostim is a recombinant Fc-fusion protein with two domains: a peptide that binds to the TPO receptor and activates intracellular signaling pathways for thrombopoiesis regulation, and a carrier antibody with a crystallized fragment domain that undergoes endothelial recycling, thereby prolonging the drug half-life (Vishnu and Aboulafia 2020). There are cytoplasmic, transmembrane and extracellular domains in the c-MPL receptor of thrombopoietin. Romiplostin binds to the extracellular domain of the receptor (Zotova et al. 2017). It dose-dependently increases platelet counts both in healthy people and ITP patients. JAK2/STAT5 are the main signal pathways for thrombopoietin receptor functioning; they induce the transcription of genes involved in platelet proliferation. Romiplostim is able to activate JAK2/STAT5, as well as PI3K/Akt, ERK and STAT3 signaling pathways, causing megakaryocytic colony-forming cells to differentiate into mature megakaryocytes and not undergo apoptosis (Fig. 2). The number of platelets in Romiplostim use begins to increase about the 5th day and reaches a peak after 10 days (Al-Samkari et al. 2020).

Romiplostim has a mean half-life of 3.5 days in the dose 3-15 mcg/kg. The peak concentration of Romiplostim is observed on average 14 hrs after injection (Al-Samkari et al. 2020). The drug is produced in the form of a lyophilized powder, the solution of which is injected subcutaneously once a week in the in-patient department. The Romiplostim efficacy in pediatric ITP has been evaluated in randomized trials. A phase I/II study in patients with ITP<18 years of age, in which patients received Romiplostim (n=17) or placebo (n=5) weekly for 12 weeks, showed the drug effectiveness and the achievement of platelet levels ≈ 50×10^9/L during the first 2 weeks of treatment. This effect was achieved in 88% of patients treated with Romiplostim. The Phase III, double-blind, placebo-controlled study included 62 children with ITP. The platelet response rate was significantly higher in the Romiplostim group (72%) compared to the placebo group (20%) (Al-Samkari et al. 2020; Suntsova et al. 2020).

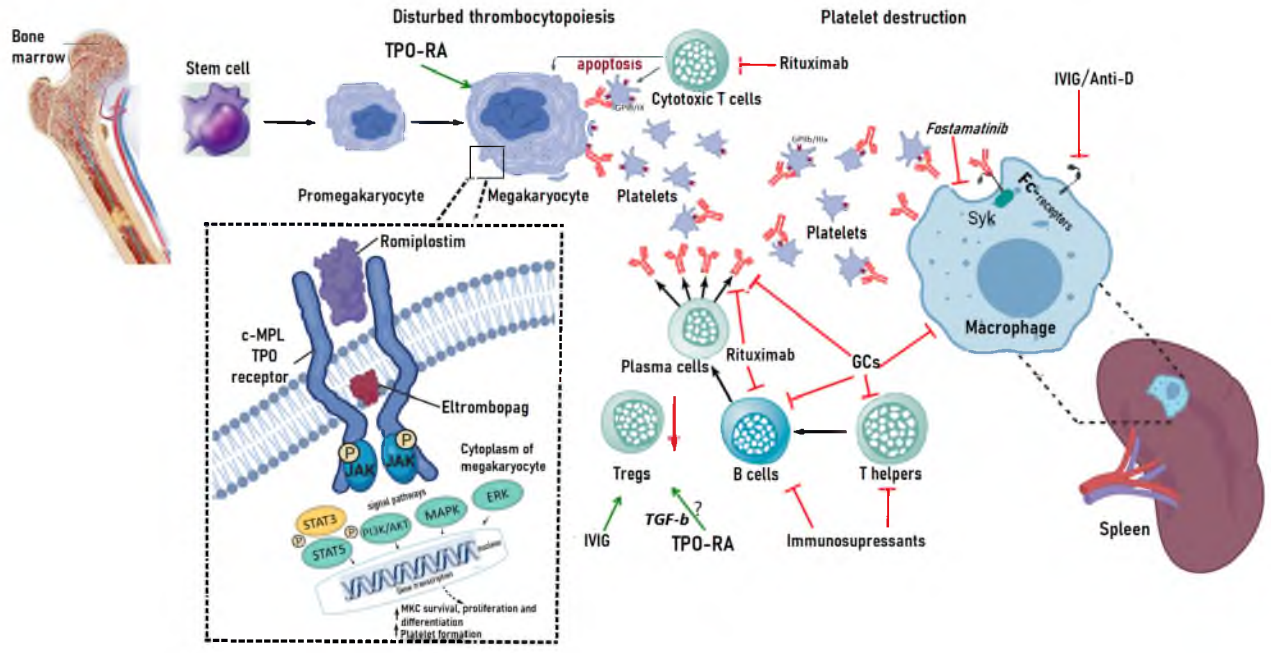


Figure 2. Targets for action of drugs used for immune thrombocytopenia (partially according to Kim)

Romiplostim is given at a dose of 1 to 10 mcg/kg subcutaneously once a week. The initial dose is 1 mcg/kg, it is increased weekly by 1 mcg/kg until the platelet count is > 50×10^9/L. Discontinuation of Romiplostim due to failure is recommended if the platelet count does not rise sufficiently after 4 weeks of treatment at the maximum dose (10 mcg/kg). However, it must be taken into account that the addition of GCs, in particular Prednisolone, in patients who have not previously the platelet response from treatment, can often lead to the positive dynamics (Al-Samkari et al. 2020).

The possibility of earlier use of Romiplostim (within the first 6 months of diagnosis) in children with ITP has been studied recently (Grainger et al. 2021). The result of the clinical study was that 93% of patients had a positive platelet response, 32% were in remission (Suntsova et al. 2020; Zotova et al. 2017; Yudina et al. 2019; Reiser et al. 2022).

The main adverse effects of Romiplostim are headache, dizziness, fatigue, epistaxis (nosebleed), diarrhea, inflammation of the upper respiratory tract, bone pain, joint pain, and muscle spasms (Vishnu and

Aboulafia 2016). A rare but potential adverse effect in long-term use of Romiplostim is an increase in bone marrow reticulin followed by fibrosis (myelofibrosis) (Al-Samkari et al. 2020). The lack of information on long-term safety data for Romiplostim in children limits its use in pediatrics (Vishnu and Aboulafia 2016).

Eltrombopag is the second currently available TPO receptor agonist. It is a small molecule that binds to the transmembrane domain of the thrombopoietin receptor. The drug interaction with the thrombopoietin receptor causes conformational changes in the structure of the latter. Through activation of the JAK2/STAT5 signaling pathways, Eltrombopag increases the platelet count by accelerating the proliferation of their precursors – megakaryocytes (Dogan et al. 2022). Both Eltrombopag and Romiplostim have been shown to have an immunomodulatory effect. It is assumed that the immunomodulatory effect of aTPO-R is mediated by transforming growth factor beta (TGF-β) – a cytokine involved in the development of Treg and found in large numbers in megakaryocytes and platelets. Eltrombopag may also interfere with MKC antigen processing and presentation (Ghanima et al. 2019).

Eltrombopag has been approved for pediatric practice in children ≥1 year of age with chronic ITP refractory to other treatments since August 2015. The starting dosage of Eltrombopag is 50 mg per day. If a positive clinical and laboratory response is not observed within two weeks after the start of treatment, the dose should be increased to 75 mg per day (Ghanima et al. 2019; Giordano et al. 2020).

The characteristic of Eltrombopag is the ability to chelate extracellular and intracellular calcium, as well as remove iron from cells. The iron-chelating effect contributes to the stimulation of stem cells in vivo. At the same time, an unexpected complication can be observed as a result of iron chelation – inhibition of cytokine secretion by T cells (Kuter 2022). In some cases, Eltrombopag as iron chelator can provoke iron deficiency anemia in children with ITP (Cooper and Cines 2019; Al-Samkari et al. 2020).

The relative advantage of Eltrombopag over Romiplostim is oral route of administration (Table 1). However, Eltrombopag absorption is sharply reduced by divalent calcium or magnesium cations, as well as dietary fats, which should be avoided in relation to the drug intake. For proper absorption of Eltrombopag, it should be taken at least 2 hrs before or 4 hrs after taking any medications or products containing polyvalent cations (antacids, calcium-rich foods, mineral supplements) (Singh et al. 2021).

Adverse effects of Eltrombopag include hepatotoxicity, which requires regular liver enzyme monitoring and the risk of cataracts (were identified in preclinical trials, but have almost no confirmation in clinical practice) (Ghanima et al. 2019). However, if patients have absorption problems or marked elevated liver enzymes, Romiplostim should be preferred over Eltrombopag (Ghanima et al. 2019).

Currently one of the main disadvantages of TPO-R agonists is their high cost (Avxentyeva et al. 2013). Pharmacoeconomic studies in Russia have shown that the total cost of therapy for one adult patient with cITP for one year with Romiplostim is 3,895,692 rubles compared with the cost of Eltrombopag therapy – 1,788,537 rubles (Krysanov et al. 2017). In the latest study, which took into account not only cost-effectiveness, but also budget impact analyses, it was found that the costs required to achieve a platelet response with Romiplostim therapy were lower – 2,400,000 rubles in comparison with Eltrombopag therapy – 2,900,000 rubles (Zhuravleva et al. 2022). The pharmacoeconomic study of TPO-RA in pediatric patients is very relevant.

Table 1. Comparative characteristics of thrombopoietin receptor agonists (adapted from Ganima et al. 2019)

Thrombopoietin receptor agonists	Romiplostim	Eltrombopag
INN	Romiplostim	Eltrombopag
Brand names	Enplate (Amgen Europe B.V., Netherlands) Romy (Intas Pharmaceuticals Ltd, India)	Revolade (Novartis, Switzerland) Promakta (Novartis, USA) Eltrombopag -29F (29 February Ltd, Russia)
Nature and binding site in TPO-R	Peptide agonist, binding to extracellular TPO-R domain	Non-peptide small-molecule agonist, binding to transmemtrane TPO-R domain
Endogenous TPO influence	Can displace TPO from its receptor	No displacement of TPO, may be additive
Signal pathways participating in thrombopoiesis regulation by drugs	JAK2/STAT5 PI3K/Akt ERK STAT3	JAK2/STAT5 ERK
Effect on MKC	Mature MKC ($CD41^+$ $CD61^+$)	Earlier MKC (including $CD41^-$) and late MKC
Other effects (off-target)	–	Chelation of Iron and Calcium
Drug form, doses available in Russia, route of administration, use frequency	Lyophilized powder for making solution for injection, 250 mcg subcutaneous once per week	Coated tablets 25 mg, 50 mg oral once per day
Limit price according to the unified information system in the field of procurement in Russia at the end of 2022	Nplate 1 vial (250 mcg) – 34,891 rub. 4 vial – 139,564 rub.	Revolade tablets 25 mg (1 box, 28 tab) – 53,279 rub. tablets 50 mg (1 box, 28 tab) – 95,457 rub.

The bioequivalent generics of TPO-RA may increase their availability for patients with ITP (Solodovnikov et al. 2020). The wider use of TPO-RA will provide more data about their mechanism of action, efficacy and safety.

At present, the Russian generic Eltrombopag – Eltrombopag-29F (February 29 Ltd) is registered. Although its selling price, presented in the state register of medicines, is 37% lower than the price of the original drug (Revolade, Novartis), it cannot be considered that this completely solves the issue of Eltrombopag high cost.

The efficacy and safety of generic Romiplostim manufactured in India (Romy, Intas Pharmaceuticals Ltd) was evaluated in children with persistent and chronic ITP from 2019 to 2020. Patients received Romiplostim for 20 weeks at a dose of 5 mcg/kg/week. The study showed that generic Romiplostim is effective and well tolerated in children with ITP as the original drug. It has been shown that a sustained platelet response after dose reduction and Romiplostim discontinuation was observed in 22 of 40 children (Mareddy et al. 2022).

Approximately one-third of patients discontinue TPO-RA because of a lack of platelet response (Cuker et al. 2022). However, if one TPO-RA does not work, replacing it with another TPO-RA may be effective (Scaramucci et al. 2014; Ghanima et al. 2019).

The experience with TPO-RA use demonstrates relatively good tolerability of both Romiplostim and Eltrombopag (Donyush et al. 2015). Their adverse event profile is rated as acceptable (Rumyancev and Maschan 2015). Both drugs have been studied in randomized, placebo-controlled clinical trials and are evidence level A drugs. Compared to some other drugs used in ITP, thrombopoietin receptor agonists do not have an immunosuppressive effect. At the same time, these drugs often do not eliminate the fatigue symptom of ITP, which makes it impossible to claim about the desired health-related life quality in ITP patients (Rovó et al. 2022).

The potential adverse effects, such as uncontrolled stem cell proliferation and the risk of myelofibrosis in use of TPO-RA, have not been proven. However, mild non-progressive reticulin fibrosis is rarely possible. A serious adverse effect of TPO-RA, mainly in adult patients, is a higher risk of thrombosis (Ghanima et al. 2019; Tjepkema et al. 2022). The incidence of thromboembolic complications was assessed in a meta-analysis of eleven studies, during which no statistically significant difference was found in thrombosis risk for patients receiving aTPO-R treatment compared with ITP patients not receiving such drugs (Tjepkema et al. 2022). In children, the risk of thrombotic complications is low. Venous thrombosis of the brain sinuses is an extremely rare, but possible adverse effect of TPO-RA use in ITP patients. Two of such cases have been reported with Eltrombopag (Teekaput et. al. 2022). New challenges have appeared with the coronavirus infection in patients with chronic ITP while taking TPO-RA (Pantic et al. 2022; Suvajdzic-Vukovic et al. 2022).

A key and unresolved issue in the TPO-RA use is the time when drugs can be discontinued in ITP patients, particularly in children. A dose reduction is recommended in those patients who achieve a stable platelet count of more than 50-100 × 10^9/L within 3-6 months (especially when using low doses of TPO-RA). Discontinuation of TPO-RA should be carried out gradually, increasing the interval between doses until the platelet count remains > 30x10^9/L. Primary results about ability of one-third of patients receiving TPO-RA to maintain a safe platelet count during the gradual drug withdrawal were surprising (Cuker et al. 2022). Remission without treatment needs to be studied and may be related to the restoration of immune tolerance. Activity restoration of not only megakaryocytes, but also of stem cells is not excluded, as shown with Eltrombopag for the severe aplastic anemia treatment, restoration of hemoglobin levels and leukocyte counts (Provan and Semple 2022).

The platelet reaction after the TPO-RA discontinuation in children is being studied. A multicenter retrospective study was conducted in children with chronic ITP with dose reduction and TPO-RA discontinuation in patients who achieved a sustained complete response. The study included ten patients (Eltrombopag n = 6, Romiplostim n = 4). Treatment was discontinued after a mean dose reduction time of 7.6 months. Two patients relapsed (median follow-up 24 of months). Overall, it has been concluded that slow dose reduction and TPO-RA withdrawal can be safely performed in pediatric patients with chronic ITP after achievement of sustained complete response (Solsona et al. 2022).

There is evidence of Romiplostim and Eltrombopag influence on health of babies born from cITP women to whom TPO-RA was prescribed during pregnancy (Payandeh et al. 2018; Michel et al. 2020). Eltrombopag use in the first trimester, with increasing the dose with pregnancy period, allowed for a natural birth without platelet transfusion. No newborns (6 cases) showed malformation, although the use of Eltrombopag was carried out before pregnancy and throughout pregnancy or from the first trimester. No cases showed maternal liver enzymes or abnormal platelet counts, including neonatal thrombocytosis (Shibata et al. 2022). More such studies and a prospective international registry are needed to monitor whether TPO-RA in wider use may lead to maternal or neonatal complications (Michel et al. 2020).

Other small molecule thrombopoietin receptor agonists (Avatrombopag, Lusutrombopag and Getrombopag) are used with limitations in adults or are in clinical trials.

Avatrombopag, an oral thrombopoietin receptor agonist, has been approved for use in the USA since 2018 in adult cITP patients with chronic liver disease comorbidity. This drug helps to increase the platelet count, which subsequently eliminates the need for

platelet transfusion and reduces the bleeding risk. Clinical trials are under way in the USA to evaluate Avatrombopag efficacy and safety in children with ITP (Kuter 2022). Unlike Eltrombopag, absorption of Avatrombopag is not reduced by dietary fats or divalent cations, and there is no need to follow dietary recommendations. Another advantage compared to Eltrombopag is the absence of necessity to monitor liver function tests, dose adjustment in patients with liver failure, and the cataract risk. Adverse effects of Avatrombopag include fever, abdominal pain, headache, nausea, swelling of the upper and lower extremities (Cheloff and Al-Samkari 2019).

Lusutrombopag, an oral aTPO-R (not registered in the Russian Federation), has been used in Japan since 2015 for the treatment of cITP patients with chronic liver disease who are scheduled to undergo invasive medical or dental procedures. It is believed that Lusutrombopag use will reduce the need for platelet transfusion and urgent hemostatic therapy in patients with cITP during surgical interventions. Lusutrombopag is taken once per day for 8-14 days before the expected date of surgical treatment at 3 mg/day. The drug absorbtion, as well as for Avatrombopag, does not depend on food intake (Alhouri et al. 2020).

Structurally modified Eltrombopag to improve efficacy and reduce adverse effects, under the name of Getrombopag, is being investigated in clinical trials only in adult ITP patients in China (Mei et al. 2022).

Since the main mechanism of TPO-RA action is the effect on megakaryocyto- and thrombopoiesis, their immunomodulatory effect with the weakening of platelet destruction is assumed, but not completely known, there are competitive directions for the new drug search for ITP treatment. They are under development or in various stages of clinical trials. Fostamatinib, a splenic tyrosine kinase (syk) inhibitor reducing antibody-dependent platelet phagocytosis, was approved in the USA in 2018 for the treatment of chronic ITP in adults. Several Fc receptor blockers are included in trials in adults with persistent and chronic ITP. Two of them (Rozanolixizumab and ARGX-117 Efgartigimod) have completed phase II clinical trials (Ghanima et al. 2019). In addition, Rilzabrutinib, a Bruton's tyrosine kinase inhibitor (BTKI), which inhibits Fc signaling, reduces platelet phagocytosis and autoantibody production, is promising (Provan et al. 2022); and Sutimlimab Anti-C1s, which reduces complement-dependent cytotoxicity, thereby reducing platelet destruction (Audia and Bonnotte 2021).

Conclusion

The thrombopoietin receptor agonists Romiplostim and Eltrombopag, which have become available for pediatric practice, deserve attention due to their efficacy and relative safety in ITP. Severe ITP requiring constant pharmacotherapy in combination with resistance or a partial, short-term platelet response with the first-line therapy (repeated courses of GCs and IVIG) are the reasons for initiating a therapy with TPO-RA. Nowadays TPO-RA are used not only in chronic ITP relapses; there is a trend towards their earlier use. Limited courses of TPO-RA may be given to children with severe newly diagnosed ITP, children with refractory ITP, persistent ITP, to avoid recurrent major bleeding and improve the effectiveness of first-line therapy. Earlier use of Romiplostim or Eltrombopag is believed to prevent the adverse effects associated with GC use and reduce the need for other subsequent treatments. All studies using Romiplostim or Eltrombopag in ITP have demonstrated a platelet response between 50-80%, depending on the criteria used. Unfortunately, despite the declared efficacy of TPO-RA therapy, some patients do not achieve or lose platelet response and have to consider another effective therapy. At the same time, the absence of cross-resistance between Romiplostim and Eltrombopag makes it possible, in case of therapeutic inefficiency of one of these two drugs, to use the other, which is associated with some differences in their pharmacodynamics (the site of binding to the thrombopoietin receptor, the effect on endogenous TPO, MKC, signaling pathways). The choice between the two TPO-RA currently available in children, Eltrombopag and Romiplostim, is often determined by the need for dietary restrictions and daily use of Eltrombopag versus parenteral administration and more frequent visits to the doctor with Romiplostim, as well as differences in drug costs.

The duration of drug use among children with ITP and platelet response after TPO-RA discontinuation remain unresolved issues. Not only the main effect – stimulation of megakaryocytosis and thrombocytopoiesis, but also the immunomodulatory effect of TPO-RA allows, with the gradual withdrawal of drugs, maintaining a stable platelet response in some patients. The safety of TPO-RA in patients with a heterogeneous orphan disease, which is ITP, requires further study.

One of the key factors limiting the use of TPO-RA is their high cost. Currently, due to the expired patents for the original drugs of TPO-RA, it is possible to reproduce them. New generics appear, including Russian generic Eltrombopag. Pharmacoeconomic studies are needed to determine the cost-benefit ratio of early use of TPO-RA versus other approaches in the treatment of ITP, especially in pediatric practice.

Conflict of interests

The authors declare no conflict of interests.

References

- Alhouri N, Imawari M, Izumi N, Osaki Y, Ochiai T, Kano T, Bentley R, Trevisani F (2020) Lusutrombopag is safe and efficacious for treatment of trombocytopenia in patients with and without hepatocellular carcinoma. Clinical Gastroenterology and Hepatology 18: 2600–2608. https://doi.org/10.1097/01.HS9.0000561072.99657.03
- Al-Samkari H, Grace RF, Kuter DJ (2020) The role of romiplostim for pediatric patients with immune thrombocytopenia. Therapeutic Advances in Hematology 11(1): 1–13. https://doi.org/10.1177/2040620720912992 [PubMed] [PMC]
- Audia S, Bonnotte B (2021) Emerging therapies in immune thrombocytopenia. Journal of Clinical Medicine 10: 1004. https://doi.org/10.3390/jcm10051004 [PubMed] [PMC]
- Avxentyeva MV, Omelyanovsky VV, Gerasimova KV (2013) Economic analysis of romiplostim (nplate) for treatment of adults with chronic immune thrombocytopenia in Russia. Medical Technologies Assessment and Choice [Meditsinskie Tekhnologii. Otsenka i Vybor] 11(1): 14–21. [in Russian]
- Ayad N, Grace RF, Al-Samkari H (2022) Thrombopoietin receptor agonists and rituximab for treatment of pediatric immune thrombocytopenia: A systematic review and meta-analysis of prospective clinical trials. Pediatric Blood & Cancer 69(3): e29447. https://doi.org/10.1002/pbc.29447 [PubMed]
- Bredlau AL, Semple JW, Segel GB (2011) Management of immune thrombocytopenic purpura in children. Pediatric Drugs 13: 213–223. https://doi.org/10.2165/11591640-000000000-00000 [PubMed]
- Cheloff AZ, Al-Samkari H (2019) Avatrombopag for the treatment of immune thrombocytopenia and thrombocytopenia of chronic liver disease. Journal of Blood Medicine 10(1): 313–321. https://doi.org/10.2147/JBM.S191790 [PubMed]
- Clinical guidelines – Immune thrombocytopenia – 2021-2022-2023 (10.11.2021) Approved by the Ministry of Health of the Russian Federation 40 p. [in Russian]
- Cooper N, Cines BD (2019) The child with immune thrombocytopenia: to treat or not to treat, is that still the question? Haematologica 104(11): 2132–2134. https://doi.org/10.3324/haematol.2019.229179 [PubMed] [PMC]
- Cuker A, Lal L, Roy A, Elliott C, Carlyle M, Martin C, Haenig J, Viana R (2022) Thrombopoietin receptor agonist discontinuation rates and reasons among patients with immune thrombocytopenia: a study of administrative claims linked with medical chart review. Annals of Hematology 101(9): 1915–1924. https://doi.org/10.1007/s00277-022-04888-7 [PubMed]
- Dogan EE, Turan Erkek E, Elverdi T, Celik Kamaci S, Ciftci U, Demirel N, Aydin D, Eren R (2022) Eltrombopag in the treatment of immune thrombocytopenia: Two-center experience from Istanbul. Indian Journal of Hematology and Blood Transfusion 38(2): 327–332. https://doi.org/10.1007/s12288-021-01462-5 [PubMed]
- Donyush EK, Soboleva VA, Malkova OV (2015) Using Romiplostim in treatment children with immune thrombocytopenic purpura resistant to corticosteroid (CS) therapy. Disease Treatment and Prevention [Lechenie i Profilaktika] 3(15): 33–38. [in Russian]
- Ghanima W, Cooper N, Rodeghiero N, Godeau B, Bussel J (2019) Thrombopoietin receptor agonists: ten years later. Haematologica 104(6): 1112–1123. https://doi.org/10.3324/haematol.2018.212845 [PubMed] [PMC]
- Giordano P, Lassandro G, Barone A, Barone A, Cesaro S, Fotzi I, Giona F, Ladogana S, Miano M, Marzollo A, Nardi M, Notarangelo LD, Pession A, Ruggiero A, Russo G, Saracco P, Spinelli M, Tolva A, Tornesello A, Palladino V, Vecchio G (2020) Use of Eltrombopag in children with chronic immune thrombocytopenia (ITP): A real life retrospective multicenter experience of the Italian association of pediatric hematology and oncology (AIEOP). Frontiers in Medicine 7(1): 1–7. https://doi.org/10.3389/fmed.2020.00066 [PubMed] [PMC]
- González-López TJ, Provan D (2022) proposal for a new protocol for the management of immune thrombocytopenia (ITP). Advances in Therapy 39(6): 2287–2291. https://doi.org/10.1007/s12325-022-02133-1 [PubMed]
- Grainger JD, Kühne T, Hippenmeyer J, Cooper N (2021) Romiplostim in children with newly diagnosed or persistent primary immune thrombocytopenia. Annals of Hematology 100: 2143–2154. https://doi.org/10.1007/s00277-021-04590-0 [PubMed] [PMC]
- Gudbrandsdottir S, Leven E, Imahiyerobo A, Lee KS, Bussel J (2020) Combination of thrombopoietin receptor agonists, immunosuppressants and intravenous immunoglobulin as treatment of severe refractory immune thrombocytopenia in adults and children. British Journal of Haematology 189(1): e31–e67. https://doi.org/10.1111/bjh.16426 [PubMed]
- Zhuravleva MV, Bessemeltsev SS, Khimich TV, Gagarina YuV (2022) Comparative pharmacoeconomic analysis of romiplostim and eltrombopag for the chronic idiopathic thrombocytopenic purpura in Russian Federation. Medical Technologies. Assessment and Choice [Meditsinskie Tekhnologii. Otsenka i Vybor] 44(2): 52–61. https://doi.org/10.17116/medtech20224402152 [in Russian]
- Kim TO, Despotovic JM (2021) Pediatric immune thrombocytopenia (ITP) treatment. Annals of Blood 6: 4. https://doi.org/10.21037/aob-20-96
- Kontievsky IN, Golenkov AK (2019) Efficacy of agonists thrombopoetin receptor: Romiplostim, Eltrombopag in patients with recurrent primary immune thrombocytopenia. The Bulletin of Hematology [Vestnik Gematologii] 15(4): 8–13. [in Russian]
- Krysanov IS, Zyryanov SK, Krysanova VS (2017) Pharmacoeconomic study of the use thrombopoietin receptor agonists in adult patients with chronic idiopathic thrombocytopenic purpura in Russian Federation. Russian Journal of Hematology and Transfusiology [Gematologiya i Transfuziologiya] 62(1): 20–25. https://doi.org/10.18821/0234-5730-2017-62-1-20-25 [in Russian]
- Kuter DJ (2022) The structure, function, and clinical use of the thrombopoietin receptor agonist avatrombopag. Blood Reviews 53: 100909. https://doi.org/10.1016/j.blre.2021.100909 [PubMed]
- Long M, Kalish LA, Neufeld EJ, Grace RF (2012) Trends in anti-D immune globulin for childhood immune thrombocytopenia: usage, response rates, and adverse effects. American Journal of Hematology 87(3): 315–317. https://doi.org/10.1002/ajh.22261 [PubMed] [PMC]
- Mageau A, Terriou L, Ebbo M, Souchaud-Debouverie O, Orvain C, Graveleau J, Lega JC, Ruivard M, Viallard JF, Cheze S, Dossier A, Bonnotte B, Perlat A, Gobert D, Costedoat-Chalumeau N, Jeandel PY, Dernoncourt A, Michel M, Godeau B, Comont T (2022) Splenectomy for primary immune thrombocytopenia revisited in the era of thrombopoietin receptor agonists: New insights for an old treatment. American Journal of Hematology 97(1): 10–17. https://doi.org/10.1002/ajh.26378 [PubMed]
- Mareddy C, Kalra M, Sachdeva A (2022) Generic romiplostim for children with persistent or chronic immune thrombocytopenia: Experience from a tertiary care centre in North India. British Journal of Haematology 197(5): 618–626. https://doi.org/10.1111/bjh.18126 [PubMed]
- Mei H, Chen X, Zhou J, Luo J, Shi Q, Liu J, Wu D, Chen G, Tai Y, Xiong J, Zou J, Hu Y (2022) Safety and efficacy of hetrombopag in patients with chronic immune thrombocytopenia: a single-arm, open-label, multi-center

phase 1 study. Annals of Translational Medicine 10(2): 30. https://doi.org/10.21037/atm-21-4361 [PubMed] [PMC]

- Melikyan AL, Pustovaya EI, Tsvetaeva NV (2018) National clinical guidelines for the diagnosis and treatment of primary immune thrombocytopenia (idiopathic thrombocytopenic purpura) in adults. Clinical Guidelines. Protocols of Treatment, 67 pp. [in Russian]
- Michel M, Ruggeri M, Gonzalez-Lopez TJ, Alkindi S, Cheze S, Ghanima W, Tvedt T, Ebbo M, Terriou L, Bussel JB, Godeau B (2020) Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study. Blood 136(26): 3056-3061. https://doi.org/10.1182/blood.2020007594 [PubMed]
- Miltiadous O, Hou M, Bussel JB (2020) Identifying and treating refractory ITP: difficulty in diagnosis and role of combination treatment. Blood 135(7): 472–490. https://doi.org/10.1182/blood.2020006529 [PubMed] [PMC]
- Neunert C, Vesely SK, Terrell DR, Arnold DM, Mithoowani S, Kim T (2019) American Society of Hematology 2019 guideline for immune thrombocytopenia. Blood Advances 3 (23): 3829–3866. https://doi.org/10.1182/bloodadvances.2019000966 [PubMed] [PMC]
- Nolla M, Aladjidi N, Leblanc T, Fernandes H, Ducassou S, Fahd M, Barlogis V, Michel M, Blouin P, Jeziorski E, Benadiba J, Pondarre C, Leverger G, Pasquet M (2021) Thrombopoietin receptor agonists as an emergency treatment for severe newly diagnosed immune thrombocytopenia in children. Blood 137(1): 138–141. https://doi.org/10.1182/blood.2020006807 [PubMed]
- Park YH, Kim DY, Kim S, Choi YB, Shin DY, Kim JS, Lee WS, Mun YC, Jang JH, Lee JW, Kook H, on behalf of Korean Aplastic Anemia Working Party (2022) Management of immune thrombocytopenia: 2022 update of Korean experts recommendations. Blood Research 57(1): 20–28. https://doi.org/10.5045/br.2022.2022043 [PubMed] [PMC]
- Payandeh M, Karami A, Karami N (2018) Romiplostim: Successful treatment of a pregnant woman with refractory immune thrombocytopenia. Biomedical Research and Therapy 5(8): 2565–2571. https://doi.org/10.15419/bmrat.v5i8.465 [FullText]
- Petrov VY (2016) Intravenous immunoglobulins – the drug of choice in treatment of immune thrombocytopenic purpura in children. Pediatrics [Pediatriya] 95(4): 36–41. [in Russian]
- Pizzi M, Vianello F, Binotto G, Vianelli N, Carli G, Auteri G, Nichele I, Sbaraglia M, Zoletto S, Scarmozzino F, Bresciani R, d'Amore F, Friziero A, Guzzardo V, Bertozzi I, Famengo B, d'Amore ESG, Sabattini E, Dei Tos AP (2022) Thrombopoietin receptor agonists increase splenic regulatory T-cell numbers in immune thrombocytopenia. British Journal of Haematology 198(5): 916–922. https://doi.org/10.1111/bjh.18309 [PubMed]
- Propaedeutics of childhood diseases textbook (2021), Kildiyarova RR, Makarova VI (Eds) 3rd edition, revised and supplemented by Borodulina TV, Galaktionova MYu, Ermakova MK, Ivanov DO, Kildiyarova RR, Legonkova TI. LLC GEOTAR-Media Publishing Group, 520 pp. https://doi.org/10.33029/9704-6612-4-PDB-2022-1-520. [in Russian]
- Provan D, Semple JW (2022) Recent advances in the mechanisms and treatment of immune thrombocytopenia. EBioMedicine 76: 103820. https://doi.org/10.1016/j.ebiom.2022.103820 [PubMed]
- Provan D, Newland AC (2022) Investigational drugs for immune thrombocytopenia. Expert Opinion on Investigational Drugs 31(7): 715–727. https://doi.org/10.1080/13543784.2022.2075340 [PubMed]
- Reiser M, Josten KM, Dietzfelbinger H, Seesaghur A, Schill M, Hippenmeyer J, Welslau M (2022) Romiplostim for primary immune thrombocytopenia in routine clinical practice: results from a multicentre observational study in Germany. Acta Haematologica 145(4): 394–403. https://doi.org/10.1159/000521689 [PubMed] [PMC]
- Rovó A, Cantoni N, Samii K, Rüfer A, Koenen G, Ivic S, Cavanna D, Benz R (2022) Real-world impact of primary immune thrombocytopenia and treatment with thrombopoietin receptor agonists on quality of life based on patient-reported experience: Results from a questionnaire conducted in Switzerland, Austria, and Belgium. PLoS One 17(4): e0267342. https://doi.org/10.1371/journal.pone.0267342 [PubMed]
- Rumyancev AG, Maschan AA (2015) Federal`ny`e klinicheskie rekomendacii po diagnostike i lecheniyu immunnoj trombocitopenicheskoj purpury` u detej. Nacional`noe obshhestvo detskix gematologov, onkologov. Natsional'nyy Meditsinskiy Issledovatel'skiy Tsentr Detskoy Ghematologii, Onkologii i Immunologii imeni Dmitriya Rogacheva Minzdrava Rossii [Federal Clinical Guidelines on Diagnosis and Treatment of Immune Thrombocytopenic Purpura in Children. Federal State Budgetary Institution "National Association of Pediatric Haematologists and Oncologists, National Medical Research Center for Pediatric Hematology, Oncology and Immunology named after Dmitry Rogachev" of the Ministry of Health of the Russian Federation. [in Russian]
- Scaramucci L, Giovannini P, Tendas A, Tendas A, Perrotti A, De Fabritiis P (2014) Reciprocal absence of cross-resistance between eltrombopag and romiplostim in two patients with refractory immune thrombocytopenic purpura. Blood Transfusion 12(1): 605–607. https://doi.org/10.2450/2014.0246-13 [PubMed] [PMC]
- Shabanov PD, Vorobieva VV (2020) Klinicheskaya Farmakologiya [Clinical Pharmacology]. Art Express, S-Petersburg, 696 pp. [in Russian]
- Shibata S, Misugi T, Nakane T, Hino M, Tachibana (2022) Use of Eltrombopag for the first trimester pregnancy complicated with refractory idiopathic thrombocytopenic purpura: a case report and literature review. Cureus 14(2): e22505. https://doi.org/10.7759/cureus.22505 [PubMed]
- Singh A, Uzun G, Bakchoul T (2021) Primary immune thrombocytopenia: novel insights into pathophysiology and disease management. Journal of Clinical Medicine 10: 789. https://doi.org/10.3390/jcm10040789 [PubMed] [PMC]
- Solodovnikov AG, Sorokina EYu, Morkovin EI (2020) Thrombopoietin receptor agonists: clinical use and evaluation of treatment efficacy. The Bulletin of the Scientific Centre for Expert Evaluation of Medicinal Products [Vedomosti Nauchnogo Tsentra Ekspertizy Sredstv Meditsinskogo Primeneniya] 10(4): 236–243. https://doi.org/10.30895/1991-2919-2020-10-4-236-243 [in Russian]
- Solsona M, Berrueco R, Sebastián E, Cervera Á, Sastre A, Astigarraga I, Argilés B, Dasí MÁ, Dapena JL, Monteagudo E (2022) Tapering of the thrombopoietin receptor agonist in paediatric patients with chronic immune thrombocytopenia: Is it possible? British Journal of Clinical Pharmacology 88(9): 4220–4223. https://doi.org/10.1111/bcp.15378 [PubMed]
- Suntsova EV, Ignatova AA, Pshonkin AV, Serkova IV, Maschan AA, Novichkova GA, Panteleev MA (2017) Dynamics of platelet functional activity and hemostatic status in a child with chronic immune thrombocytopenia on romiplostim treatment. Pediatric Hematology/Oncology and Immunopathology [Voprosy Ghematologii/Onkologii i Immunopatologii v Pediatrii] 16(3): 69–72. https://doi.org/10.24287/1726-1708-2017-16-3-69-72 [in Russian]
- Suntsova EV, ChikvinaII, Sadovskaya MN, Kotskaya NN, Hachatryan LA, Baydildina DD, Kalinina II, Petrova UN, Pshonkin AV, Lutfullin IY, Lemazina EN, Osipova IV, Galeeva AV, Naumova OS, Fisyn IV, Bikova GV, Kazaryan GR, Maschan AA, Novichkova GA (2020) Use of romiplostim for newly diagnosed immune thrombocytopenia in children. Pediatric Hematology/Oncology and Immunopathology [Voprosy Ghematologii/Onkologii i Immunopatologii v Pediatrii] 19(1): 18–26. https://doi.org/10.24287/1726-1708-2020-19-1-18-26 [in Russian]
- Suvajdzic-Vukovic N, Virijevic M, Pravdic Z, Sabljic N,

Adzic-Vukicevic T, Mitrovic M (2022) Coronavirus disease 2019 in patients with chronic immune thrombocytopenia on thrombopoietin receptor agonists: new perspectives and old challenges. Blood Coagulation & Fibrinolysis 33(1): 51–55. https://doi.org/10.1097/MBC.0000000000001109 [PubMed]

- Teekaput C, Nadsasarn A, Tanprawate S, Soontornpun A, Thiankhaw K, Wantaneeyawong C, Teekaput K, Chai-Adisaksopha C (2022) Cerebral venous sinus thrombosis in immune thrombocytopenia patients treated with thrombopoietin receptor agonist: Case reports and literature review. Annals of Medicine and Surgery 79: 104116. https://doi.org/10.1016/j.amsu.2022.104116 [PubMed] [PMC]
- Tjepkema M, Amini S, Schipperus M (2022) Risk of thrombosis with thrombopoietin receptor agonists for ITP patients: A systematic review and meta-analysis. Critical Reviews in Oncology/ Hematology 171: 103581. https://doi.org/10.1016/j.critrevonc.2022.103581 [PubMed]
- Vianelli N, Auteri G, Buccisano F, Carrai V, Baldacci E, Clissa C, Bartoletti D, Giuffrida G, Magro D, Rivolti E, Esposito D, Podda GM, Palandri F (2022) Refractory primary immune thrombocytopenia (ITP): current clinical challenges and therapeutic perspectives. Annals of Hematology 101(5): 963–978. https://doi.org/10.1007/s00277-022-04786-y [PubMed] [PMC]
- Vishnu P, Aboulafia DM (2016) Long-term safety and efficacy of romiplostim for treatment of immune thrombocytopenia. Journal of Blood Medicine 7: 99–106. https://doi.org/10.2147/JBM.S80646 [PubMed] [PMC]
- Warrier K, Chauhan A (2012) Management of immune thrombocytopenic purpura: An update. The Ochsner Journal 12(3): 221–227. https://doi.org/10.2165/11591640-000000000-00000 [PMC]
- Williams K (2016) Use of intravenous Anti-RhD Immunoglobulin (RhIG) in the treatment of primary immune thrombocytopenia. Clinical Laboratory Science 29(2): 92–97. https://doi.org/10.29074/ascls.29.2.92
- Yasser A, Khasahba EO, Shokeir M, Mabood S (2020) Treatment lines of childhood chronic ITP: A retrospective single-center analysis. Pediatric Hematology/Oncology and Immunopathology [Voprosy Ghematologii/Onkologii i Immunopatologii v Pediatrii] 19(3): 26–30. https://doi.org/10.24287/1726-1708-2020-19-3-26-30 [in Russian]
- Yudina NB, Belyanskaya MV, Solovyova MA, Trubnikova GV, Ryabova EA, Ovchinnikova YuS, Orlova EA, Skorobogatova DA, Brezhneva NV, Ryabova SA, Bykova IL, Sargina EV, Shtokalov AA, Stepanova TV, Grebennikova IV (2019) Experience in the treatment of immune thrombocytopenia in the Department of Oncohematology of Voronezh Regional Children's clinical hospital № 1. The Russian Journal of Pediatric Hematology and Oncology [Rossijskij zhurnal detskoj gematologii i onkologii] 1(6): 28–38. https://doi.org/10.21682/2311-1267-2019-6-1-28-38 [in Russian]
- Zotova II, Gritsaev SV, Bessmeltsev SS (2017) Primary immune thrombocytopenia. The current understanding of the pathogenesis and treatment. The Bulletin of Hematology [Vestnik Ghematologii] 13(4): 48-63. [in Russian]
- Zotova II, Sergeev VG (2018) Pathogenetic justification for the therapy of idiopathic thrombocytopenic purpura (primary immune thrombocytopenia) in adults. Kazan Medical Journal [Kazanskii Meditsinskii Zhurnal] 99(2): 279-286. https://doi.org/10.17816/KMJ2018-279 [in Russian]

Author contributions

- **Olga S. Levchenkova**, Doctor Habil. of Medical Sciences, Associate Professor, Department of Pharmacology, e-mail: os.levchenkova@gmail.com, **ORCID ID** https://orcid.org/0000-0002-9595-6982. The author had a leading role in the planning, information searching, interpretation of the obtained material, drafting the article and its translation into English.
- **Viktoriya V. Vorobieva**, Doctor Habil. of Medical Sciences, Senior Lecturer, Department of Pharmacology, e-mail: v.v.vorobeva@mail.ru, **ORCID ID** https://orcid.org/0000-0001-6257-7129. The author analyzed the literature and participated in the data interpreting, and writing the final version of the article.
- **Vasiliy E. Novikov**, Doctor Habil. of Medical Sciences, Professor, Head of Department of Pharmacology, e-mail: novikov.farm@yandex.ru, **ORCID ID** https://orcid.org/0000-0002-0953-7993. The author was engaged in structuring the article and consulted on writing the final version of the article.
- **Tatiana I. Legonkova**, Doctor Habil. of Medical Sciences, Professor, Head of Department of Pediatrics Employment, e-mail: legonkova@yandex.ru, **ORCID ID** https://orcid.org/0000-0001-9401-2579. The author consulted on the research idea, concept and pediatric aspects.
- **Elena N. Volkova**, Resident of the Department of Neonatology and Pediatrics, e-mail: elena.iwanczowa-lena@yandex.ru, **ORCID ID** https://orcid.org/0000-0001-8979-3454. The author participated in information searching, interpretation of the obtained data, and drafting the article.