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REVIEW ARTICLE

Diagnosis and treatment of immune thrombocytopenia in Poland

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Abstract

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by an isolated platelet count of less than 100,000/μL caused by destruction and reduced production of platelets. Systemic steroid therapy is a mainstay of first-line treatment; however, additional treatment lines are usually necessary due to the very high recurrence rate after therapy completion and steroid resistance. Standard treatment options for steroid resistance or steroid dependence include splenectomy, rituximab or thrombopoietin receptor agonists.

The article presents current data on the diagnosics and therapy of ITP, considering the limited access to some forms of treatment in Poland.

Keywords: idiopathic thrombocytopenic purpura, steroid-resistant, steroid-dependent, TPO-RA, splenectomy, rituximab

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Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by an isolated platelet count of less than 100,000 per μL caused by destruction and reduced production of platelets [1, 2]. The annual incidence is estimated at 2–5/100,000 [3–5]. The clinical manifestation of the disease is very heterogenous with a broad spectrum of symptoms, from asymptomatic cases, through the symptoms of bleeding diathesis affecting the skin and mucosa, to rarely occurring severe gastrointestinal and intracranial bleeding [2, 6]. Low platelets count in ITP patients weakly correlates with the severity of bleeding diathesis symptoms. The tolerance of severe thrombocytopenia is greater than that of central thrombocytopenia, which is related to the higher haemostatic efficiency of young platelets. In most cases, symptoms other than skin and mucosal ecchymosis are absent and severe, and life-threatening bleeding is quite rare. Intracranial bleedings and major mucosal bleedings occur in approximately 1.4% and 9.5% of ITP patients, respectively [7–10].

ITP can be subcategorized into primary (idiopathic, approx. 80%) and secondary form (approx. 20%), resulting from taking medications and vaccines or other underlying medical conditions [1, 5]. The most common causes of secondary ITP are shown in Table 1.

Depending on the duration of the symptoms, ITP could be classified as newly diagnosed (< 3 months), persistent (3–12 months) and chronic (> 12 months). While there is a high tendency to spontaneous remissions in paediatric patients (> 50%), in adult patients this percentage is about 10%, and the disease becomes chronic, characterized by flare-ups with periods of remission in between [1, 6, 11, 12].

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Table 1. Common causes of secondary immune thrombocytopenia

Drugs/vaccines	MMR vaccine
Autoimmune diseases	Systemic lupus erythematosus (SLE) Antiphospholipid syndrome (APS) Evans syndrome
Infections	Human immunodeficiency virus (HIV) Hepatitis C virus (HCV) Helicobacter pylori
Cancers	Chronic lymphocytic leukaemia (CLL), more rarely other indolent lymphoproliferative diseases
Other	Primary immunodeficiencies Status after allogeneic haematopoietic stem cell transplantation

Diagnostics

The diagnosis is made by excluding other causes of thrombocytopenia. Diagnostics include complete blood count (CBC) along with peripheral blood smear (PBS), typically revealing isolated thrombocytopenia, the presence of giant platelets, and increased mean platelet volume. In some cases, anaemia with features of iron deficiency (sideropenia) may be present. The severity of anaemia should be adequate to the severity of the bleeding disorder. A reticulocyte count and assessment of iron metabolism parameters may be helpful in differentiation.

The indications for bone marrow trephine biopsy are limited to cases in which it is difficult to rule out another cause of thrombocytopenia. It should be considered in patients over 60 years of age (excluding myelodysplastic syndrome) and in patients with other CBC abnormalities or systemic symptoms.

Throughout the diagnostic process, it is also necessary to exclude infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), and Helicobacter pylori. It is also recommended to measure serum immunoglobulins (IgG, IgM and IgA) levels to diagnose common variable immunodeficiency (CVID), to perform a pregnancy test in women of childbearing age, thyroid function tests, and direct antiglobulin test (DAT). The remaining tests are useful in the presence of symptoms that may indicate other disorders leading to thrombocytopenia.

Determining anti-platelet antibodies titer is not recommended due to the low sensitivity and specificity of this test [1, 2].

Treatment

Systemic glucocorticosteroids (GCs) are used as first-line treatment in patients with a newly diagnosed ITP. The answer to the question of which patient qualifies for treatment, and whether to start treatment in an outpatient or inpatient setting, is ambiguous and should depend on several factors. Consideration should be given to comorbidities, patient's age, presence of bleeding diathesis symptoms, the need to use anticoagulant/antiplatelet drugs, patient's preferences and, finally, confidence in the accuracy of diagnosis.

A platelet count of less than 30 G/L is considered an indication for treatment initiation in asymptomatic patients or patients with mild cutaneous and mucosal bleeding diathesis. In 2019, the American Society of Haematology (ASH) expert panel confirmed this position in its recommendations, suggesting the introduction of first-line treatment in asymptomatic patients with a platelet count below 30 G/L [1].

The standard of treatment is prednisone at a daily dose of 0.5–2.0 mg/kg body weight (bw) or dexamethasone at a daily dose of 40 mg in 4–day pulses repeated 4–6 times. Both drugs show similar effectiveness. Platelet count recovery is observed faster after dexamethasone, however, in patients over 60 years of age and diabetic patients, prednisone may be the preferred drug.

Treatment duration should not exceed six weeks. If remission has not been achieved within this timeframe, it is very unlikely to achieve it with prolonged steroid therapy, and the risk of treatment-related complications becomes very high [1, 13–15].

An alternative form of first-line treatment is a 1 g/kg bw infusion of intravenous immunoglobulin (IVIg) for two consecutive days or 0.4 g/kg bw for five days in older adults who may not tolerate large single doses of IVIg. In the case of severe bleeding, both forms of therapy (GCs and IVIg) can be combined. Platelet transfusions should remain reserved for patients with life-threatening bleeding. Some experts recommend in such situations continuous platelet infusion.

There is a lack of studies directly comparing steroid therapy with observation in patients with no or mild cutaneous and mucosal bleeding symptoms with platelet count exceeding 30 G/L. There was no evidence of an increased risk of major bleeding, which is 0.9% and 0% for steroid therapy and the watch-and-wait strategy, respectively. Due to

the risk of serious side effects of systemic steroid therapy such as weight gain, hypertension, hyperglycaemia, steroid-induced cataracts, sleep and mood disorders, steroid myopathy, osteoporosis, gastritis, and gastric ulceration, as well as the lack of clear treatment benefits with low risk of severe bleeding, it is recommended to adopt a wait-andsee attitude in this group of patients [1].

If the platelet count is below 20 G/L, it is suggested to start treatment in a hospital setting Hospitalization allows for confirming a diagnosis, establishing management, observing the early response to treatment, and assessing comorbidities that increase the risk of major bleeding. Patients with a previously confirmed diagnosis of ITP and a platelet count lower than 20 G/L can be treated on an outpatient basis, but are subject to regular follow-up by an experienced haematologist, which is often unattainable in Polish conditions.

Due to the very low percentage of patients achieving sustained remission (around 10%), second-line therapy is required in most cases. First-line therapy failure is defined as the maintenance of a platelet count of 30 G/L after three months of treatment or the need to repeat steroid therapy courses due to the recurrence of thrombocytopenia [1].

Currently, there are three basic options for second-line treatment — splenectomy, thrombopoietin receptor agonists (TPO-RA) and rituximab.

There is no single preferred second-line therapy for all patients with chronic or persistent ITP. Randomized trials directly comparing all three modalities are lacking. The response rate after 1 month is 86.7%, 65.7% and 62.1% for splenectomy, TPO-RA and rituximab, respectively. The sustained response rates are estimated at 53%, 63.2%, and 39.4%, respectively. There was no significant difference in the incidence of major bleeding in patients after splenectomy, treated with TPORA and receiving rituximab (4.6%, 3.5%, 2.2%, respectively). Splenectomy is associated with an approximately 12.8% risk of serious postoperative complications. The rate of infectious complications is also higher and amounts to 10%, 6.9% and 3.7%, respectively, for patients treated with splenectomy, TPO-RA and rituximab [1, 16–28].

As spontaneous remission is possible within the first year of the disease, splenectomy is not recommended for patients with persistent ITP (3–12 months). In such situations, the ASH expert panel suggests TPO-RA therapy rather than rituximab, although the final choice should depend

on the patient's preferences, availability of drugs (rituximab is not reimbursed in Poland in such an indication) and possible coexisting diseases [1].

There are two TPO-RA treatments currently available — romiplostim and eltrombopag. Both drugs do not show any significant difference in both the response rate and response durability. However, they differ in the route and frequency of administration. Eltrombopag is an oral drug taken at a daily dose of 25–75 mg. Romiplostim is a drug administered subcutaneously at a dose of 1–10 μg/kg bw once a week. In some patients taking eltrombopag, a mild and transient elevation of transaminases level is usually observed. The choice between these drugs should depend mainly on the patient's preferences [1, 16–20]. In Poland, TPO-RA treatments are reimbursed under the National Health Fund drug program. According to this, romiplostim is reimbursed only for patients refractory to first-line treatment and not achieving remission after splenectomy. The eligibility criteria for eltrombopag treatment were extended to include the group of patients in whom the local team consisting of a haematologist, anaesthesiologist and surgeon found contraindications for splenectomy. Due to the lack of reimbursement of rituximab in this indication, access to modern forms of treatment is therefore limited to patients with existing contraindications to splenectomy. In these patients eltrombopag therapy is possible. The remaining patients are forced to use other forms of treatment, covering the entire spectrum of immunosuppressive and immunomodulating drugs. However, this treatment is less effective and associated with a higher risk of serious side effects (Table 2) [21].

In patients with chronic ITP (> 12 months), the ASH expert panel in its 2019 recommendations suggests the use of TPO-RA rather than rituximab, and rituximab rather than splenectomy [1, 22–28]. This suggestion is driven by a higher risk of infectious complications and the risk of perioperative and postoperative splenectomy complications. Additionally, it is necessary to remember the necessity to conduct additional vaccinations before, as well as anti-infective surveillance and prophylaxis after splenectomy [1, 22–25].

When making therapeutic decisions in this group of patients, patient's preferences and priorities should also be considered. For patients who prioritize a long-term response, splenectomy or TPO-RA should be recommended. For patients wishing to avoid surgery, either TPO-RA treatment

Table 2. Immunosuppressants/immunomodulators used in immune thrombocytopenia

Drug	Dosage
Azathioprine	Max. 150 mg/d.
Cyclosporine	5 mg/kg bw/d for 6 days, then
	2.5–3 mg/kg bw/d with target serum drug concentration of 100–200 ng/mL
Mycophenolate mofetil	250–1000 mg/d for 4–6 weeks
Danazol	200 mg 2–4 times daily
Vincristine	1–2 mg once a week for a total dose of 6 mg
Cyclophosphamide	1–2 mg/kg p.o. for 16 weeks or 0.3–1.0 g/m2 p.c., 1–3 doses every 2–4 weeks

bw — body weight; p.c. — percutaneously — przeskórnie; p.o. — per os

or rituximab (not reimbursed in Poland) seems to be a good option. For patients wishing to avoid chronic medication use, splenectomy or rituximab is recommended. In this group of patients, the reimbursement of TPO-RA treatments is also limited to patients for whom splenectomy failed (romiplostim and eltrombopag), with extension to patients with contraindications to splenectomy (eltrombopag).

Despite the aforementioned therapeutic options, there is still a need to develop new therapies dedicated to patients with a resistant form of ITP. In addition to the next TPO-RA generations, such as avatrombopag, there are currently ongoing clinical trials evaluating molecules with different mechanisms of action. An example is fostamatinib, which is a spleen tyrosine kinase (Syk) inhibitor. Its activation by binding the Fc domain of IgG to the macrophage receptor causes the initiation of platelet phagocytosis. Of the 146 patients participating in the myOpportuniTy3 study, 44% had a platelet count of more than 50 G/L. The proportion of patients who achieved a sustained response (sustained platelet count > 50 G/L) was 17%. In patients who responded but did not achieve a durable response, in most cases platelet counts remained at a level above 30 G/L, with rare fluctuations below this value [29]. Another drug currently under investigation is rozanolixizumab. It is a subcutaneously administered humanized monoclonal antibody against neonatal receptors for the Fc domain of IgG (FcRn, neonatal Fc receptor). By blocking the FcRn, pathogenic autoantibodies are not protected by the receptor against catabolism and are thus degraded faster, resulting in a rapid reduction in IgG levels. In phase II clinical trial, more than half of the 66 patients receiving rozanolixizumab achieved platelet counts above 50 G/L. This effect became apparent eight days after subcutaneous administration of the drug and lasted from 10 to 35 days depending on the dosing regimen [30].

Summary

Immune thrombocytopenia is an acquired autoimmune disease characterized by an isolated platelet count of less than $100,000/\mu L$ caused by destroying and reduced production of platelets. The clinical manifestation covers a broad spectrum of symptoms, from asymptomatic cases, through the symptoms of bleeding diathesis affecting the skin and mucosa, to rarely occurring severe gastrointestinal and intracranial bleeding.

The diagnosis is made by excluding other causes of thrombocytopenia. Diagnostics include complete blood count along with peripheral blood smear, typically revealing isolated thrombocytopenia, the presence of giant platelets, and increased mean platelet volume. The indications for bone marrow trephine biopsy are limited to cases in which it is difficult to rule out another cause of thrombocytopenia. It should be considered in patients over 60 years of age (excluding myelodysplastic syndrome) and in patients with other abnormalities of peripheral blood or systemic symptoms.

The first-line treatment is systemic steroid therapy with prednisone (0.5–2.0 mg/kg bw) or dexamethasone (40 mg/day for 4 days in 4–6 pulses). Due to the very small percentage of patients achieving durable remission, in most cases, second-line therapy is required. First-line therapy failure is defined as maintaining of platelet count less than 30 G/L after three months of treatment or the need to repeat steroid therapy courses due to recurrent thrombocytopenia.

We currently have three basic second-line options — splenectomy, TPO-RA treatments, and rituximab. Splenectomy is not recommended in patients with persistent ITP (3–12 months) due to the possibility of spontaneous remission within the first year of the disease. In such situations, TPO-RA treatment is suggested rather than rituximab, although the final choice should depend on the patient's preferences, availability of drugs and possible coexistence of other diseases. In Poland, TPO-RA treatments are reimbursed under the NHF drug program for patients with insufficient response to first-line pharmacotherapy and after the failure of splenectomy, defined as platelet

count less than 30 G/L. The eligibility criteria for eltrombopag were extended to include patients with contraindications for splenectomy confirmed by a team consisting of a haematologist, surgeon and anaesthesiologist. Due to significant limitations in the reimbursement of modern therapies (no reimbursement of rituximab, restricted availability of TPO-RA), a large group of patients is treated with classic immunosuppressants, which does not comply with universal standards of ITP therapy. Alternative therapies with drugs such as fostamatinib and rozanolixizumab are still under clinical trials.

Conflict of interest

The authors declare no conflict of interest.

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