New Developments in the Pathophysiology and Management of Primary Immune Thrombocytopenia

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Hämostaseologie

Abstract

Immune thrombocytopenia (ITP) is an autoimmune disease that is characterized by a significant reduction in the number of circulating platelets and frequently associated with bleeding. Although the pathogenesis of ITP is still not completely elucidated, it is largely recognized that the low platelet count observed in ITP patients is due to multiple alterations of the immune system leading to increased platelet destruction as well as impaired thrombopoiesis. The clinical manifestations and patients' response to different treatments are very heterogeneous suggesting that ITP is a group of disorders sharing common characteristics, namely, loss of immune tolerance toward platelet (and megakaryocyte) antigens and dysfunctional primary hemostasis. Management of ITP is challenging and requires intensive communication between patients and caregivers. The decision to initiate treatment should be based on the platelet count level, age of the patient, bleeding manifestation, and other factors that influence the bleeding risk in individual patients. In this review, we present recent data on the mechanisms that lead to platelet destruction in ITP with a particular focus on current findings concerning alterations of thrombopoiesis. In addition, we give an insight into the efficacy and safety of current therapies and management of ITP bleeding emergencies.

Keywords

- platelet immunology
- immune thrombocytopenia
- autoantibodies
- autoimmune diseases

Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune bleeding disorder characterized by bleeding due to isolated thrombocytopenia with platelet count less than 100×10^9/L.[1–4] The incidence of ITP ranges between 3.3 and 3.9/100,000 per year in adults, and between 1.9 and 6.4/100,000 per year in children.[3,5] The exact mechanism of the immune repsonse toward own cells (autoimmunity) leading to TIP are incompletely understood, but includes an alteration of the balance between effectors and regulatory cells.[6] This imbalance results in a breakdown of the immune tolerance causing increased platelet clearance and impaired thrombopoiesis. For a long time, it was thought that the low platelet count is solely caused by enhanced destruction of platelets opsonized by antiplatelet antibodies.[7–9] However, recent studies have shown that T-cell cytotoxicity and impaired megakaryopoiesis are additional pathomechanisms in ITP.

While a brief course with spontaneous remission is frequently observed in the majority of children with ITP, most adult patients display chronic ITP which can be associated with clinically significant bleeding, including hemorrhages in skin or mucous membranes such as petechiae, purpura, and rarely intracranial manifestations.[10,11] Based on these clinical symptoms, the primary therapeutic aim in ITP is to reduce the risk of severe bleeding and not necessarily to increase platelet count. According to the International Working Group,[2,12] newly diagnosed patients with ITP who are at low risk of bleeding can be safely managed with observation (wait and see strategy), while those with severe chronic

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thrombocytopenia or at higher risk of bleeding require urgent treatment.

This review explores the mechanisms leading to platelet destruction in ITP with a particular focus on current findings concerning alterations of thrombopoiesis. In addition, we will address common questions about therapy for ITP, including when to treat/when not to treat, efficacy and safety of therapies, management of ITP bleeding emergencies, and unique treatment considerations.

New Insights into the Pathophysiology of Immune Thrombocytopenia

The loss of immunological tolerance to autoantigens expressed on patients' own platelets has been identified as one of the critical issues in the pathophysiology of ITP. In this context, several studies reported T-cell abnormalities with an imbalance in T helper (Th)1:Th2 ratio in ITP patients.[13,14] Dysfunction of these cells is thought to be responsible for increased number and activity of cytotoxic T lymphocytes. This increased activity contributes directly to the increased platelet destruction as well as improved survival of B-cell. These B-cells with enhanced survival produce autoantibodies against platelet leading to accelerated platelet clearance. Upon binding of these autoantibodies, platelets were eliminated through phagocytosis, apoptosis, complement activation, and impairment of platelet production.[15,16] While these Fc-mediated mechanisms seem to predominantly induce platelet destruction in the spleen, recent studies proposed new Fc-independent mechanisms.[17–19] ITP autoantibodies were shown to induce glycan modification of platelet surface glycoproteins (GPs), which are recognized by Ashwell-Morell receptors, expressed on hepatocytes, leading to accelerated platelet clearance in the liver.[20] In some patients, this may explain the ineffectiveness of splenectomy which represents the last ITP therapeutic option for refractory subjects. Interestingly, 2 years later, a retrospective study involving 61 ITP patients reported a correlation between platelets desialylation and a reduced response to first-line treatments corroborating the hypothesized Fc-independent mechanism.[21,22] Another Fc-independent mechanism has been suggested by Quach et al who showed that nonresponding ITP patients often produce autoantibodies targeting the ligand-binding domain (LBD) of GPIb/IX. This specific binding can activate GPIb/IX by platelet receptor crosslinking, inducing unfolding of its mechanosensory domain and the consequent platelet destruction.[23] Recently, we showed that patients with autoantibodies who can induce desialylation in platelet and megakaryocytes have more sever course of ITP.[24] The use of sialidase inhibitor treatment in combination with other therapies might be a promising approach to increase platelet count in some patients who have failed previous therapies.

The platelet life cycle is regulated by the intrinsic apoptotic pathway similar to nucleated *B-cells*. Considering this, the contribution of ITP autoantibodies in inducing platelet apoptosis was investigated by several groups using well-defined apoptosis markers such as depolarization of the mitochondrial transmembrane potential, Bcl-2 family protein expression, caspase-3 and -9 activation, and phosphatidylserine exposure.[25,26] Apoptosis in platelets from pediatric and adult patients was ameliorated by immunoglobulin infusion.[27,28] Interestingly, in a recent study, apoptotic platelets were found in ITP patients expressing anti-GPIIb/IIIa and anti-GPIb autoantibodies but not in those carrying anti-GPIa/IIa autoantibodies.[29] This suggests a possible preferential specificity of the autoantibodies in inducing platelets apoptosis. Although the exact mechanism of autoantibody-mediated platelet apoptosis is not completely known currently, these findings suggest a relevant contribution of the apoptotic pathway in the ITP pathogenesis, opening novel horizons for deeper investigations.

Autoantibody binding also results in suppression of megakaryocyte maturation and platelet formation.[30,31] The antibody-mediated inhibition of platelet production was demonstrated by in vitro studies showing impaired megakaryocyte maturation and decreased platelet formation.[32–34] An interesting open question is, however, the role of megakaryocyte apoptosis in the ITP pathophysiology. Controversial results were presented in several studies during the last few years. In fact, it has been reported that ITP plasma can reduce megakaryocyte apoptosis.[35] In particular, after cultivation of human stem cells (HSCs) from healthy umbilical cord blood with ITP plasma, a decreased percentage of apoptotic cells, reduced expression of tumor necrosis factor–related apoptosis inducing ligand, and increased expression of the antiapoptotic protein Bcl-xL have been observed in the differentiated megakaryocytes.[36] In contrast, an in vivo study published by Houwerzijl et al showed that megakaryocytes undergo apoptosis in the presence of autoantibodies displaying nuclear fragmentation, chromatin condensation, and activation of caspase 3, in biopsies of ITP patients, leading to phagocytosis of the polyploid cells by macrophages residing in the bone marrow.[37] A more recent study showed increased megakaryocyte apoptosis in bone marrow samples of ITP patients.[38]

Diagnosis

The diagnosis of ITP is often based on the exclusion of other causes of thrombocytopenia.[2,12,39] Diagnosis can be made in patients with platelet count less than 100,000/µL who lack findings that suggest another diagnosis in their history, physical examination, complete blood cell count, and blood smear. Identifying alternative causes of thrombocytopenia can, however, be difficult and requires comprehensive expertise in platelet disorders. Detection of a characteristic autoantibody proves the diagnosis of ITP. Although many guidelines consider further laboratory testings unnecessary, positive results obtained in GP-specific assays such as direct monoclonal Antibody-specific Immobilization of Platelet Antigen (MAIPA) or direct immunobead assay prove the diagnosis of ITP.[40] However, due to the lack of a strong evidence for clinical advantage, current guidelines from the 2019 American Society of Hematology (2019 ASH) do not give a clear recommendation for antibody evaluation in ITP.[4] Testing of the presence of platelet autoantibodies should be performed as part of the initial assessment, as a positive test

result establishes a sound basis for further diagnostic procedures and treatment. Despite the excellent specificity of the test, a significant drawback of direct GP-specific tests is their low sensitivity, and a negative test result has no relevance. It is therefore useful to establish a diagnosis of (primarily) hyperdestructive thrombocytopenia early in the patient's assessment.

Treatments

Active Bleeding

Reported rates of severe bleeding vary depending on the population studied. A recent systematic review including 118 studies with 10,908 ITP patients revealed a rate of intracranial hemorrhage (ICH) of 1.0% (95% confidence interval [CI]: 0.7–1.3). Deaths due to bleeding are rare, and overall mortality among patients with ITP is only slightly higher than age- and sex-matched controls.[41] The overall rate of non-ICH major bleeding was 15.0% (95% CI: 4.1–17.1). A more recent study used a validated ITP bleeding assessment tool to measure bleeding in ITP.[42] This study reported that 56% of ITP patients had severe bleeding at some point during their disease course, and 2% had ICH.[43]

The main aims of ITP treatment are to stop active bleeding and reduce the risk of future bleeding. Specific measures to stop bleeding should include, besides withdrawal of anticoagulant and antiplatelet agents, the administration of glucocorticoids, intravenous immunoglobulin (IVIG), and transfusion of platelet concentrate or all of these measures. However, data from randomized trials are still lacking, and the use of these treatments is supported generally by small observational studies. In addition, some limitations of these approaches should be taken into consideration. Platelet transfusions can help limit bleeding, but the effect is commonly transient, due to the rapid clearance by the autoantibodies. Thus, they should not be used alone but rather in combination with IVIG or/and glucocorticoids. IVIG raises the platelet count within 2 to 4 days in 80% of patients, but effects last only 1 to 2 weeks. Therefore, concomitant use of glucocorticoids with IVIG can be considered to achieve more sustained response than that with IVIG alone.[44] In life-threatening situations, additional treatments may be required. Drugs that may be useful in patients with ITP to control minor bleeding are tranexamic acid (particularly for mucocutaneous bleeds) and contraception (menorrhagia).[45,46] In life-threatening ITP bleeding emergencies, recombinant activated factor VII may be a useful supportive treatment.

Bleeding Prophylaxis

In asymptomatic thrombocytopenia patients and in those who have only mild mucocutaneous bleeding, a careful risk assessment of future bleeding and patient preferences should be taken into consideration in decision making for bleeding prophylaxis. However, the usefulness of current bleeding scores in clinical practice is limited by their complexity and lack of validation in large studies.[42] From a clinical point of view and despite the lack of sufficient data from prospective studies, a platelet count of less than 30,000/µL and/or comorbidity is frequently used as a reliable cut-off for treatment in adults according to the 2019 ASH guidelines.[4] However, other risk factors besides platelet count should be taken into account, such as age (e.g., >65 years), history of bleeding, concomitant use of anticoagulants and platelet inhibitors, renal or hepatic impairment, and the risk of trauma from daily activities.[47,48] It is generally recommended that patients who are receiving anticoagulants or antiplatelet agents should receive treatment to maintain platelet count above 50,000/µL.

Although the platelet count is an important marker for disease activity in ITP, the decision-making to initiate therapy should be individualized and take bleeding risk factors and patient preferences into account. Our suggested approach to first-line therapy in adults and children is summarized in ►Table 1, as well as in ►Fig. 1.

Glucocorticoids

Glucocorticoid treatment is the standard initial therapy for patients with ITP. Prednisone and dexamethasone are most commonly used agents. Prednisone is given 0.5 to 2 mg/kg orally per day for 1 to 2 weeks, with a gradual withdraw and discontinuation by 6 to 8 weeks. Dexamethasone is administrated as one or more cycles of 40 mg orally once daily for 4 days, usually 4 weeks apart. A meta-analysis of randomized trials found that platelet counts were higher at 14 days in patients receiving dexamethasone compared with patients receiving prednisone, but overall responses at 6 months did not differ significantly.[50] So, there is no clear advantage for dexamethasone over prednisone.

Although 60 to 80% of patients with ITP have an initial response to glucocorticoids, only 20 to 40% of adults have a sustained response after glucocorticoids are discontinued.[51,52] Medical therapies for patients with ITP who do not have an initial response to glucocorticoids or who have recurrent decreases in platelet count after glucocorticoids are discontinued include thrombopoietin-receptor agonists (TPO-RAs) and immunomodulators. Importantly, corticosteroids should be withdrawn rapidly and discontinued in nonresponding patients to prevent toxicities associated with prolonged corticosteroid exposure, including weight gain and osteoporosis, but result in acute toxicities including cognitive impairments, hypertension, and hyperglycemia.

Intravenous Immunoglobulin

IVIG raises the platelet count more rapidly than corticosteroids.[53] In a multicenter, randomized study of 122 adults with newly diagnosed ITP, IVIG was shown to be more effective at raising the platelet count by day 5 than corticosteroids (79 vs. 60% response rate). The guidelines from the ASH recommend that IVIG should be given initially as a single dose of 1 g/kg and repeated in nonresponding patients.[2] In fact, a randomized trial of 37 adults with ITP showed that a single IVIG dose of 1 g/kg is more likely to induce a platelet count response by day 4 compared with patients who received lower initial doses of 0.5 g/kg (67 vs. 21%),[44] indicating that an initial IVIG dose of 1 g/kg is preferred for most patients with the possibility of repeating a second dose the next day. Common side effects of

Table 1 Current therapies in adults and children with ITP according to the 2019 ASH guidelines[4]

	Adult	Children
Therapy vs. observation		
Observation	Newly diagnosed ITP and a platelet count $>30 \times 10^9$/L who are asymptomatic or have minor mucocutaneous bleeding	Newly diagnosed ITP with no or minor bleeding (recommendation with low evidence)
Therapy	Platelet count $< 30 \times 10^9$/L and/or additional comorbidities, anticoagulant or antiplatelet medications and/or upcoming procedures, and/or for elderly patients (>60 years old)	Platelet count $< 20 \times 10^9$ and non–life-threatening mucosal bleeding and/or diminished health-related quality of life
Therapy with		
Corticosteroids	Prednisone (0.5–2.0 mg/kg per day) or dexamethasone (40 mg per day for 4 days)	Prednisone (2–4 mg/kg per day; maximum, 120 mg daily for 5–7 days) rather than dexamethasone (0.6 mg/kg per day; maximum, 40 mg per day for 4 days)
IVIG	Single dose (1 g/kg) and repeated the following day in nonresponding patients. For treatment of acute bleeding or for rapid platelet count response within 12–24 h	IVIG is not recommended as first-line therapy for children except in case of major bleeding
Rituximab	Rituximab is not recommended for first-line therapy. Only if there is high evidence for remission, an initial course of rituximab in combination with corticosteroids may be preferred	Not for first-line treatment
TPO-RAs	No first-line treatment. Observational studies may have evidence for increased remission in patients with early use	
Emergency treatment	High-dose corticosteroids, IVIG, and platelet transfusions. Supportive treatments may include recombinant factor VIIa, tranexamic acid, and TPO-RAs	

Abbreviations: ASH, American Society of Hematology; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.

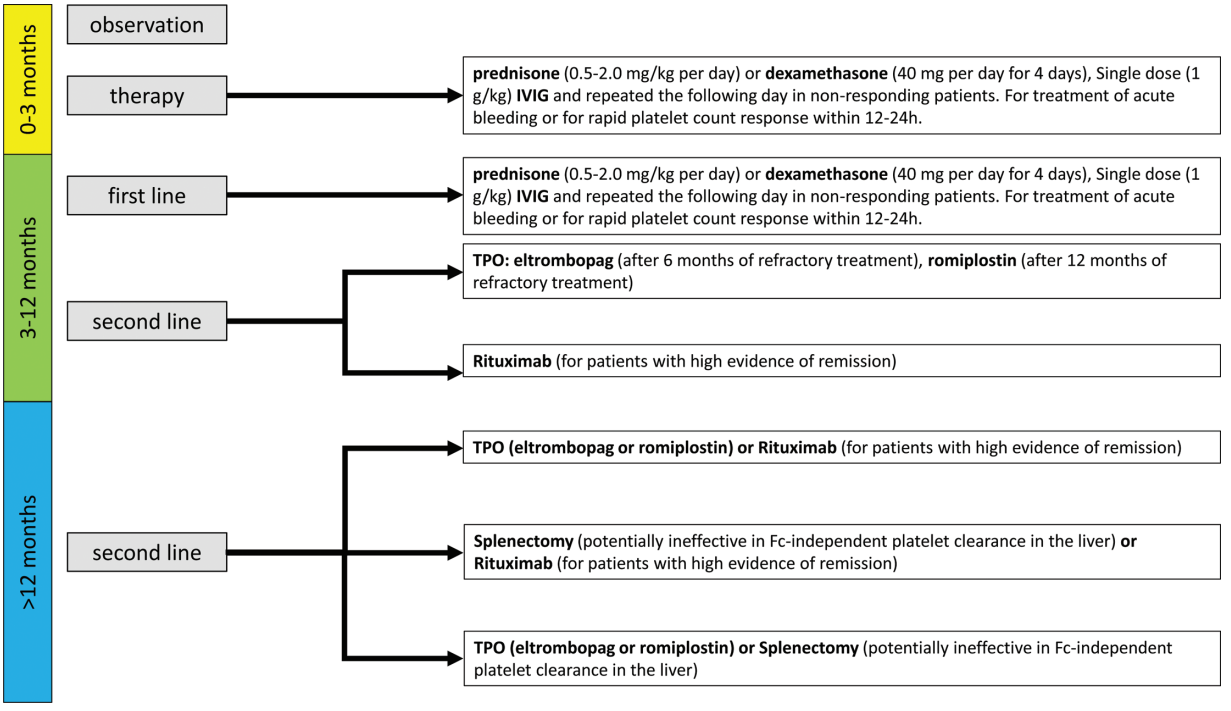

Fig. 1 Suggested algorithm to manage immune thrombocytopenia (ITP) in adults for first- and second-line therapy adapted from the guidelines of 2019 American Society of Hematology.[4] Therapeutic options differ considering the stage of disease. During the first 3 months after onset of ITP, observation rather than therapy is indicated. In second-line therapy, personalized medicine should be chosen taking comorbidities, compliance, patient values, and preferences into consideration. Contraindications, potential adverse effects, and ineffectiveness of should be carefully evaluated.[20,49]

IVIG include headache, aseptic meningitis, acute kidney injury, and hemolysis from passive transfer of anti-A and anti-B hemagglutinins in patients with non–O blood group.[54–57] Moreover, IVIG has been suggested to be associated with an increased risk of thrombosis.[58] However, a recent systematic review of 31 randomized trials did not demonstrate an increased risk of thromboembolism due to IVIG (odds ratio [OR]: 1.10; 95% CI: 0.44–2.88).[59–61]

Anti-Rh(D) Immunoglobulin

Anti-RhD Ig is thought to bind and occupy Fc receptors in the reticuloendothelial system with antibody-coated Rh(D)-positive red blood cells, thus preventing antibody-coated platelets from being destroyed.[62] Anti-RhD Ig is usually given intravenously for patients with Rh(D)-positive blood type with an intact spleen as single dose of 50 to 75 µg/kg. A safe subcutaneous administration in small children or patients is also described in the literature.[63] Side effects include mild infusion reactions such as headache, nausea, chills, fever, and mild to moderate hemolysis.[64] However, life-threatening episodes of severe intravascular hemolysis associated with anti-Rh Ig administration have been reported.[65,66] It is noteworthy to mention that, in some countries, anti-D for ITP treatment is not approved as a licensed treatment for ITP.

Thrombopoietin-Receptor Agonists

Eltrombopag and romiplostim are TPO-RAs for patients with ITP that is refractory to other treatment and with disease lasting more than 6 months (eltrombopag) or 12 months (romiplostim).[67] In randomized, placebo-controlled trials of each of these agents involving patients with chronic ITP in whom at least one previous therapy has failed, 70 to 95% of patients had an increased platelet count with initial treatment and 40 to 60% had durable responses with ongoing treatment.[68,69]

Eltrombopag is administered as a daily tablet, whereas romiplostim is administered in weekly subcutaneous injections. In Germany, TPO-RAs received approval for treatment even before splenectomy. The choice between the two agents is guided by the preferred form of administration and anticipated adherence. Interestingly, some observational data suggest that if one agent is ineffective, switching to the other results in a platelet response in up to 50% of patients.[70,71]

An initial response to TPO-RAs usually occurs within 1 to 2 weeks. Once a response is achieved, ongoing treatment is required to maintain effect. However, retrospective and prospective cohort studies have shown that 10 to 30% of patients can discontinue treatment after receiving TPO-RAs for many months or years, and the disease remains in remission, although late relapses may occur.[72,73] Although some patients seem to have a prolonged/complete remission after pausing TPO, no prognostic marker is currently available to identify such patients.

The main safety concern is an increased risk of venous thromboembolism.[74] In extension studies of both agents, thromboembolism developed in 6% of patients during a median follow-up of 2 years.[75,76]

A new oral TPO-RA is avatrombopag, which, unlike eltrombopag, can be administered without dietary restrictions. The phase 3 clinical trials showed a longer median number of weeks with platelet count of 50,000/µL or higher during the first 26 weeks in patients who received avatrombopag than in those who received placebo.[77]

Immunomodulators

Rituximab is widely used for the immunomodulation in patients with ITP, although it is not approved for this indication. In a meta-analysis including five randomized studies, significantly higher incidence of complete response at 6 months was observed with rituximab compared with glucocorticoids or placebo.[78] Of note, the response to rituximab is typically observed within 1 to 8 weeks. The main advantage of rituximab over other immunomodulators is the sustained platelet responses that last more than 2 years in 50% of patients who have a response.[79,80] An increase in minor infections has been reported with rituximab. However, major complications such as progressive multifocal leukoencephalopathy seem to be rare.[81] Taken together, due to the lower efficacy and higher complications compared with TPO-RAs,[82] rituximab should be avoided as first-line therapy and used only if there is high evidence for remission.[4]

Fostamatinib is an oral tyrosine kinase (Syk) inhibitor that can be used to treat patients with ITP in whom one previous therapy has failed. Recently, fostamatinib was shown to induce a response within 12 weeks in 43% compared with 14% of those receiving placebo. In addition, a sustained platelet count $\geq$50,000/µL for up to 24 weeks was observed in 18% of refractory ITP patients compared with 2% of those receiving placebo.[83]

Hydroxychloroquine is described as a steroid-sparing agent that can be helpful for treatment purposes. Especially in secondary ITP, it might be an option in patients with systemic lupus erythematodes. However, there is limited information on this and further studies are needed to conclude about efficacy of this treatment.[84]

Dapsone, danazol, and several immunosuppressive agents are also used in patients with ITP. However, data to support their use are largely limited to retrospective observational studies that suggest that 30 to 60% of patients have a response.

Tranexamic acid is described in two studies as highly effective in controlling menorrhagia and acute bleeding in female patients with ITP and should be taken into account in the treatment of female patients with chronic ITP.[45,46]

Splenectomy

Splenectomy remains the most effective therapy for ITP inducing long-lasting remissions in 60 to 70% of patients.[85] To reveal the site of platelet clearance is a promising predictor of therapy response, but the indium-labeled autologous platelet scanning is technically challenging and not widely available all over the world.[86] Knowledge of desialylation capacity of the antibody might also helpful to detect Fc-independent clearance of platelets in the liver.[20] Nevertheless, the potential complications of splenectomy, and the inability to predict responsiveness, is usually limited to

chronic ITP patients who do not have a response to standard medical therapies.[86,87] Short-term risks of splenectomy include operative and postoperative complications, including venous thromboembolism and sepsis. Laparoscopic splenectomy is associated with lower postoperative mortality and morbidity and a shorter recovery time than open splenectomy.[85,88] Moreover, the immediate as well as the persistent risk of venous thromboembolism has been shown to be higher among patients with ITP who have undergone splenectomy as compared with those who have not undergone splenectomy.[89,90] Besides thromboembolic complications, splenectomy is associated with an increased risk of infection with encapsulated bacteria; vascular complications, such as coronary artery disease and stroke; and chronic thromboembolic pulmonary hypertension. Thus, splenectomy is generally not recommended in frail elderly patients because of increased surgical complications in this patient population. More importantly, splenectomy should be postponed in the first 12 months.

Conclusions

ITP is a complex and multifactorial disease. Currently, there is a general consensus that the pathophysiology of ITP is caused by abnormal function of regulatory B- and T-cells leading to proliferation of platelet-specific plasma and cytotoxic cells, respectively. While the latter is responsible for a direct destruction of platelet as well as megakaryocyte in ITP, IgG autoantibodies can induce thrombocytopenia in ITP by several Fc-domain dependent and independent mechanisms including platelet phagocytosis, complement activation, apoptosis, cell lysis, and inhibition of proplatelet production. The urgent management to treat active, clinically relevant bleeding in ITP patients should include discontinuation of any anticoagulation or platelet-function inhibitors if taken, platelet transfusions, and IVIG and steroids. In acute bleeding, IVIG and corticosteroids might be more effective than platelet transfusions alone. Since a cure for ITP is currently still missing, the aim of treating ITP patients with significant bleeding tendency should be to stop bleeding (usually reaching a stable platelet count above 30,000/µL). If initial treatment with IVIG and steroids was not successful in inducing remission or if relapse occurred while withdrawing steroids, TPO-RA is recommended. Rituximab and splenectomy can be considered as alternative therapeutic strategies in refractory ITP patients.

Conflicts of Interest

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