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An update on the management of immune thrombocytopenic purpura and emerging treatment options: A review and case report

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Abstract

Immune thrombocytopenic purpura affects both children and adults. It is an autoimmune disorder characterised by persistent thrombocytopenia (peripheral platelet count of less than 150 x10^9/L) due to autoantibody binding to platelet antigen(s) causing their premature destruction by the reticulo-endothelial system, in particular the spleen. There is no gold standard diagnostic test to confirm ITP. The diagnosis of ITP remains clinical and is based principally on the exclusion of other causes of thrombocytopenia by the history, physical examination, full blood count, peripheral blood film and autoimmune screen. Medical options for front-line drug therapy are corticosteroids, intravenous immunoglobulin, and intravenous Rh anti-D. Second and third line therapy includes monoclonal antibodies and thrombopoirtin receptor agonist. Transfusion of platelet is warranted if life threatening hemorrhage occurs. This review gives a brief discussion on the pathophysiology, clinical presentation, diagnosis and treatment of Immune Thrombocutopenic Purpura and a case report.

Keywords: Immune Thrombocytopenic Purpura, Thrombocytopenia, Immunoglobulins, Monoclonal Antibodies, Thrombopoietin receptor agonist

1. Introduction

Immune thrombocytopenic purpura (ITP, also known as idiopathic thrombocytopenic purpura) is a clinical syndrome in which a decreased number of circulating platelets (thrombocytopenia) manifests as bleeding tendency, easy bruising (purpura), or extravasation of blood from capillaries into the skin and mucous membrane (petechiae). In adults, the course is commonly chronic, whereas in children its primary or acute, but most patients never experience serious bleeding even with severe thrombocytopenia. Intracranial hemorrhage may occur when the platelet count drops below $10*10^9$/L ($<10*10^3$/µL) [1].

ITP can be classified based on patient age (adult or childhood ITP), and duration of thrombocytopenia (newly diagnosed ITP or chronic) [2]. Newly diagnosed ITP is designation given for the 1st 3 months after diagnosis. Chronic ITP by definition persists for more than 12 months. In between acute and chronic category there is another entity called Persistent ITP, which is defined as ITP with low platelet count persisting for 3 to 12 months [3]. Recurrence in ITP is defined as return of symptoms after at least 3 months of remission sustained without treatment and is seen in nearly 5% of cases [4].

More than 80% of the children with untreated ITP have a spontaneous recovery with completely normal platelet counts in 2-8 weeks. Fatal bleeding occurs in 0.9% upon initial presentation [5]. Approximately 60-90% of adults with ITP respond with an increased platelet count after treatment with prednisone or prednisone and intravenous immunoglobulin (IVIG). Of those adults who do not maintain an increased platelet count and who require splenectomy, approximately two thirds have a sustained response and 10-15% have partial response [1,6].

1.1 Pathophysiology

The pathogenesis of ITP is incompletely understood. Reduced platelet lifespan due to antibody-mediated destruction, as well as impaired platelet production both contribute. The underlying mechanism is thought to involve

specific immunoglobulin G (IgG) autoantibodies produced by the patient's B cells, most often direted against platelet membrane glycoproteins such as GPIIb/IIIa[7].

Genetic and acquired factors probably contribute. Two commonly cited acquired events are infections (typically viral) and systemic conditions that disrupt immune homeostasis (eg, autoimmune disease, lymphoid malignancy).

Some cases of ITP are associated with a preceding viral infection or, less commonly, bacterial infection. Antibodies against viral antigens may cross-react with normal platelet antigens (a form of molecular mimicry). Infection with human immunodeficiency virus (HIV), Hepatitis C virus (HCV), Cytomegalovirus (CMV), and Varicella Zoster virus (VZV) have been proposed to cause secondary ITP by this mechanism [8-10].

Alteration in immune homeostasis might induce loss of peripheral tolerance and promote the development of self-reactive antibodies. Potential examples include antiphospholipid syndrome, systemic lupus erythematous, evans syndrome, hematopoietic cell transplantation, chronic lymphocytic leukemia (CLL) and other low-grade lymphoproliferative syndrome [11].

Alternative immunologic mechanisms involving T cells have also been postulated to cause ITP, including T cell-mediated cytotoxicity and defects in the number and/or function of regulatory T cells (Tregs)[12].

2.Clinical Presentation and Diagnosis

Many patients with ITP are are asymptomatic. Physical examination is mostly positive for cutaneous manifestations as petechiae, ecchymoses and bruising. One-fourth of patients present with epistaxis, although hematuria is less frequent [4]. A diagnosis of ITP is confirmed by a finding of thrombocytopenia in a blood smear. The presence of mild eosinophilia, along with a few megathrombocytes, is a common findings [13].

Peripheral Smear: Bone marrow examination is not routinely performed in children unless atypical clinical or laboratory findings are present. Tests for reticulocyte count, erythrocyte sedimentation rate, antinuclear antibodies, blood group, Coombs, and Epstein-Barr virus may be needed in selected cases depending on associated symptoms. Close and continued monitoring of clinical status and hematologic status is the most important step in managing ITP.

Coagulation studies: coagulation studies are not required in patients who have mild thrombocytopenia without clinically important bleeding. However prothrombin time (PT) and partial thromboplastin time (aPTT) are performed in individuals withmoderate to severe thrombocytopenia or with concerns about clinically important bleeding, to eliminate some potential causes of thrombocytopenia (eg, liver disease) and to elicit other potential treatable causes of bleeding(eg, vitamin K deficiency).

Bone marrow examination: This is reserved for patients for patients with other unexplained cytopenias (anemia, leucopenia), dysplasia on peripheral blood smear, or other unexpected hematological findings.

Additional Evaluations: All adult patients with newly diagnosed ITP should undergo testing for HIV and HCV. There is insufficient evidence to support the routine use of anti-platelet, antiphospholipid, and anti-nuclear antibodies, thrombopoietin levels, or platelet parameters obtained on automated analyzers in the evaluation of patients with suspected ITP[14].

3.Case Report

A 54 year old male patient came to emergency department with the complaints of tongue bleeding. He also had the complaints of reddish purpuric spot in oral mucosa and also all over the body since past few days which later developed into blisters. He was diagnosed with ITP in 2008 went to remission with a course of steroids and stopped. He didn't have any signs of ecchymoses, petechiae, and easy bruising. His complete blood count revealed a platelet count of 2000 cells/cumm at the time of admission. Peripheral smear study showed Neutrophilic Leucocytosis with marked Thrombocytipenia. Patient was started immediately with Inj. Methylprednisolone and IVIG with diagnosis of ITP. His platelet count improved gradually to 52000cells/cumm but steadily decreased following hospital discharge. IV globulin was given for first 2 days then stopped. He was also transfused with 4 pint platelet. The steroid was tapered off and patient was discharged home with an unstable platelet count on oral steroids.

3.1 Management of ITP

The goal of ITP treatment is to provide a safe platelet count to prevent clinically important bleeding, rather than to normalize the platelet count. The overall risk of bleeding in ITP is low; it is greatest in individuals with platelet count less than 10,000/microL[15].

Treatment of ITP can be divided into medical and surgical management. Medical management is further divided into first-line and second-line pharmacotherapy. Medical options for front-line drug therapy are corticosteroids, intravenous (IV) immunoglobulin (Ig), and IV Rh anti-D.

3.1.1 Management of severe or life-threatening bleeding

Emergency treatment is indicated for internal or profound mucocutaneous bleeding. Hospitalization is required, and general measures should be instituted to reduce the risk of bleeding, including avoidance of drugs that inhibit platelet function, control of blood pressure, and other factors.

Emergency treatment:

- Platelet transfusions (two platelet pools every 4-6 hours or platelet pool/h); with/without
- IVIG (1 g/kg, repeated the following day if the platelet count remains <50x109/L. Concurrent use of IVIG increases platelet life span); with/without
- Intravenous methylprednisolone, 1 g/d for 3 days [16].

3.2 First Line Treatment

Once the decision to treat a patient with ITP has been made, and provided the patient's situation is not life threatening, corticosteroids are the standard initial treatment. Intravenous immunoglobulins are generally recommended for patients with critical bleeding and for those unresponsive to corticosteroids. The platelet count also can be supported by anti-D immunoglobulin, which active in the pre-splenectomy is setting [17].

3.2.1 Corticosteroids

Corticosteroids have not been shown to alter the natural history of ITP; however, they allow the physician to "buy time" to determine which patients have acute ITP (lasting less than 6 months) and which patients will develop chronic ITP and thus potentially need additional therapy. Approximately two thirds of patients achieve a complete or partial response with corticosteroids, and most responses occur within the first week of treatment. The standard practice is to initiate treatment with oral prednisolone or prednisone, 1 to 2 mg/kg per day, given as single or divided doses. However, major variations exist in treatment regimens in reference to the duration of full-dose treatment (2- 6 weeks) and the mode of tapering (fast or slow). In our practice, we taper and discontinue prednisone over 4 weeks after achieving a normal platelet count because this period includes the time during which most spontaneous remissions would occur [17].

The mechanisms of action of corticosteroids in ITP have not been completely elucidated. It has been suggested that corticosteroids impair the clearance of antibodycoated platelets by tissue macrophages, 48 inhibit antibody production, and increase platelet production possibly by inhibiting phagocytosis of platelets by bone marrow macrophages. In addition, cutaneous bleeding may resolve before an increase in the platelet count is seen, suggesting a direct effect of corticosteroids on vascular integrity [18].

3.2.2 Intravenous Immunoglobulin (IV IgG):

IV IgG acts by impairing the clearance of opsonized platelets, probably mediated through the FccRIIb receptor. Some studies also suggest that IV IgG might cause increased clearance of antiplatelet antibodies via saturation of the neonatal Fc salvage receptor for IgG[19]. Platelet counts may begin to increase after 1 day and usually reach peak levels within 1 week after treatment. However, responses are generally transient, lasting no longer than 3 to 4 weeks, after which the platelet counts decrease to pretreatment levels [20].

IV IgG at a dose of 400mg/kg/day for 5 days or 1mg/kg/day for 2 days has been used in the management of ITP. IV IgG can induce an increase in platelet count to more than 50,000/µL. The response is usually rapid and patients achieve a platelet count more than 50,000/µL in the second and fifth day. Thus IV IgG therapy is ideal when rapid increase in blood platelet count is desired in patient with life threatening bleeding. It can also be combined with steroid and platelet transfusion in these situations. Response to IV IgG usually lasts about 3 weeks and repeate cycles are frequently needed [21].

3.2.3 Anti-D Immunoglobulin [anti-Rh(D)]

The anti-D immunoglobulin is effective only in Rh Dpositive nonsplenectomized patients, in whom the antibody binds to the erythrocyte D antigen. The mechanism of action involves immune-mediated clearance of the opsonized erythrocytes via the Fc receptors of the reticuloendothelial system, thereby minimizing removal of antibodycoated platelets [22].

Anti-D can be administered safely by intravenous injection over a few minutes. The response rate in one series was 70%, and the increase in platelet count lasted more than 3 weeks in 50% of the responders. The toxicity profile of anti-D is similar to that of IVIg. The standard dosage of 50 mg/kg per day of intravenous anti-D requires 72 hours to produce a clinically significant platelet increase. Therefore, anti-D has not been recommended as first-line therapy to rapidly elevate the platelet count in patients with severe thrombocytopenia [22].

The substantial advantages of anti-D compared with IVIg are lower costs (although still much more expensive than corticosteroids) and more convenient administration. The dose-limiting toxicity of anti-D is hemolytic anemia, with a mean decrease in hemoglobin of 1.0 g/dL, occasionally accompanied by chills and nausea. Anti-D appears to have minimal efficacy in splenectomized patients [22].

Table 1. First-Line Treatment Options

Clinical Situation	Therapy Option
Newly diagnosed ITP	• Dexamethasone • or • Prednisone (?) • Methylprednisolone • IVIg • Intravenous anti-D (Rho) immunoglobulin

Abbreviations: ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin.

Table 2. Strength of Recommendations for Second- and Third-Line Treatments in Adults With Chronic ITP

Treatments	Strength of Recommendation	
	Consensus Report	ASH Guidelines
Second-line treatments		
TPO receptor agonists	**A**	2C
Rituximab	B	2C
Splenectomy	**C**	**1B**
Third-line treatments		
TPO receptor agonists	A	1B

Table 1 and table 2 taken from: Marc Michel. Immune Thrombocytopenia Nomenclature, Consensus Reports, and Guidelines: What Are the Consequences for Daily Practice and Clinical Research? *J. Semin Hematol*. 2013. 03.008*.

3.3 Second and third-line treatment

Some patients may not have a stable, safe platelet count following therapy with glucocorticoids or intravenous immune globulins. Therapy with splenectomy or rituximab and in some cases a thrombopoietin receptor agonist or other immunosuppressive therapy is appropraiate for patients who continue to have clinically significant bleeding.

3.3.1 Splenectomy

For decades splenectomy has been considered the second-line treatment in adults with ITP unresponsive to initial corticosteroid therapy. Recently, however, the availability of effective pharmacological agents has challenged the position of splenectomy in the treatment algorithm. Two thirds of patients achieve normal platelet counts post-splenectomy with no additional therapy (time to response 1-24 days). Many of the remainder has an improvement in counts [16].

Generally accepted criteria for splenectomy include a severe thrombocytopenia (<10-20 x 10^9/L), a high risk of bleeding for platelet counts less than 30 x 10^9/L, or the requirement of continuous glucocorticoid therapy to maintain safe platelet counts. Absolute contraindications to splenectomy include a high risk for surgery (medical comorbidities)[16].

3.3.2 Rituximab

Rituximab is a chimeric monoclonal antibody directed against B cell surface protein CD20.it is thought to eliminate B cells via apoptosis, antibody-dependent cytotoxicity, and complement-mediated lysis[23].

Rituximab can be used as a single agent in patients who do not have an adequate platelet count response to glucocorticoids and splenectomy. Patients should be screened for hepatitis B infection before starting rituximab because of the higher risk of hepatitis B reactivation. Treatment with rituximab can suppress vaccine response for upto six months after the administration [24].

The dose of rituximab typically used in patients with ITP is 375mg/m^2 intravenously once a week for four consecutive weeks. Usually dosing is based on more extensive experience with it, although lower doses may be sufficient for ITP therapy compared with hematological malignancies [25].

3.3.3 Thrombopoietin (TPO) Receptor Antagonists

These act by stimulating the production of megakaryocytes and ultimately platelets in the bone marrow by binding to and activating the TPO receptor. Generally, platelet counts increase in approximately 5 days and peak at approximately two weeks from the time of starting therapy. Once treatment is discontinued, platelet counts generally return to baseline level or even below baseline (rebound thrombocytopenia) [26].

Available TPO receptor agonists include romiplastim (is administered as 1 to 10 mcg/kg once weekly subcutaneous injection) and eltrombopag (is given as a once-daily pill). The initial dose of Eltrombopag is 50 mg daily. The dose is subsequently adjusted to achieve platelet counts > 50,000/microL with goal of raising the platelet count enough to reduce the risk of bleeding rather than normalizing platelet count. Platelet should be measured weekly during initiation until a stable dose has been established, and then counts are typically measured monthly [27].

3.4 Summary of the American Society of Hematology 2011 evidence-based practice guideline for management of immune thrombocytopenia:

The goal of all treatment strategies for ITP is to achieve a platelet count that is associated with adequate hemostasis, rather than a normal platelet count. The decision to treat should involve a discussion with the patient and consideration of the severity of bleeding, anticipated surgical procedures, medication side effects, and health-related quality of life.

3.4.1 Special Considerations for Adults and Children:

Adults:

• Consider treatment for patients with a platelet count < 30 x 109/L.

• Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIg.

• IVIg may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.

• Either IVIg (1g/kg for one dose, repeated as necessary) or anti-D (in appropriate patients) may be used as a first-line treatment if corticosteroids are contraindicated.

Children:

• A single dose of IV Ig (0.8-1.0 g/kg) or a short course of corticosteroids should be used as first-line treatment.

• IV Ig should be used instead of corticosteroids if a more rapid increase in platelet count is required.

• There is no evidence to support using corticosteroids for longer courses compared to very brief courses.

• Anti-D may be considered for first-line therapy in Rh+ non-splenectomized children with recognition of the risks outlined above.

3.4.2 Special Considerations for Children and Adults:*

Choice of therapy	Children	Adults
Splenectomy	Recommended for children with significant or persistent bleeding and lack of response or intolerance of other therapies such as corticosteroids, IVIg, and anti-D, and/or who have a need for improved quality of life.	Recommended for adults who have failed corticosteroid therapy, with similar efficacy with open or laparoscopic procedures.
Rituximab	May be considered for children with ITP who have significant ongoing bleeding and/or have a need for improved quality of life despite conventional treatment. Also may be considered as an alternative to splenectomy in children with chronic ITP or as therapy in those who have failed splenectomy.	May be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy.
Thrombopoietin Receptor Agonists	Studies are ongoing, but there are no published data to guide the use of these agents in children.	Recommended for adults at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy. These agents may also be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not undergone splenectomy
High-Dose Dexamethasone	May be considered for children or adolescents with ITP who have significant ongoing bleeding and/or have a need for improved quality of life despite conventional treatment. Also may be considered as an alternative to splenectomy in children with chronic ITP or in those who have failed splenectomy.	No comment in current guidelines.
Immunosuppression	Multiple agents have been reported; however data for any one specific agent remain insufficient for specific recommendations	Multiple agents have been reported; however data for any one specific agent remain insufficient for specific recommendations.

*Of the pharmacologic options listed above, the thrombopoietin receptor agonists have FDA approval in adults with chronic ITP who have an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Dexamethasone has FDA approval for treatment of ITP in adults. All other therapies are considered off-label use.

3.4.3 Further considerations

1. Special Considerations for Secondary ITP:

Secondary ITP (HIV- associated):

• Treatment of the underlying HIV infection with antiviral therapy should be considered prior to other treatment options unless the patient has clinically significant bleeding.

• IVIg, corticosteroids, or anti-D may be used initially for patients requiring further therapy.

• Splenectomy is considered preferable to other agents in symptomatic patients who have failed initial drug therapy.

Secondary ITP (HCV- associated):

• Antiviral therapy should be considered in the absence of contraindications, but the platelet count should be closely monitored in these situations due to a risk of worsening thrombocytopenia attributable to interferon.

• If treatment is required, the initial management should be with IVIg.

Secondary ITP (H. pylori- associated):

• Routine testing for H.pylori is not recommended in asymptomatic children with unresolved ITP.

• Screening for H.pylori should be considered in adults for whom eradication therapy would be undertaken if testing were positive.

• Eradication therapy for H.pylori should be administered to patients who are found to have infection.

2. MMR-related ITP:

• Children with a history of ITP who are not immunized should receive their scheduled first MMR vaccine.

• In children with either non-vaccine or vaccine-related ITP who have already received their first dose of MMR vaccine, vaccine titers can be checked. If the child displays full immunity, no further MMR vaccine should be given. If the child does not have adequate immunity, then the child should be re-immunized at the recommended age.

3. ITP in Pregnancy:

• Pregnant patients requiring treatment should receive either corticosteroids or IVIg.

• For pregnant women with ITP, the mode of delivery should be based on obstetric indications.

4.Conclusion

The etiology of ITP may be genetic as well as acquired factors. The pathogenesis is presumed to be related to platelet destruction and/or inhibition of platelet production via the production of specific autoantibodies. Although not an uncommon entity, there is much to be learned in the diagnosis and management of ITP as well as further studies are to be carried out.

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