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Review

Pathophysiology, Diagnosis and Treatment of Immune Thrombocytopenia

Mihnea-Alexandru Găman,[1] Amelia Maria Găman[1]

Abstract

Immune thrombocytopenia (ITP) is an acquired disorder characterized by isolated thrombocytopenia with a peripheral blood count < 100.000/mm3 in the absence of any obvious initiating or underlying causes, by antibody mediated destruction of platelets and suppression of megakaryocyte and platelet production on the basis of immune deregulation. ITP is idiopathic (primary) in 80% of cases and secondary to several associated disorders in 20% of cases. A diagnosis of exclusion, based on patient history, physical examination, complete blood count and examination of the peripheral blood smear, is used for ITP. The treatment of ITP is indicated in adult patients with platelet counts below 20.000-30.000/mm3, with bleedings or risk for bleeding. First line therapy is represented by corticosteroids, intravenous immunoglobulins and intravenous anti-RhD. Second-line treatment is represented by: splenectomy, inhibition of the monocytic phagocytic system therapy, immunosupressive therapy, anabolic steroids, anti-CD20 therapy, and thrombopoietin receptor agonists.

Keywords: primary immune thrombocytopenia, ITP, guidelines, thrombopoietin receptor agonists, splenectomy, immune thrombocytopenic purpura.

About the author: *Mihnea-Alexandru Găman is currently a 4th year medical student of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania of a six year program. He is currently working on a research project concerning the molecular analysis of the Factor VIII (F8) gene, funded by the Society of Students in Medicine of Bucharest (SSMB).*

Introduction

Immune thrombocytopenia (ITP) is an acquired disorder characterized by isolated thrombocytopenia with a peripheral blood count < 100.000/mm3 in the absence of any obvious initiating or underlying causes. 1 Immune thrombocytopenia may be idiopathic (primary) in 80% of cases and secondary to several associated disorders in 20% of cases: chronic or acute infections, vaccination, autoimmune disorders, immunodeficiency diseases, lymphoproliferative diseases, drugs. The Immune Thrombocytopenia International Working Group consensus divided the disease into three phases: newly diagnosed ITP (less than 3 months from diagnosis), persistent ITP (between 3 months - one year from diagnosis) and chronic ITP (more than one year from diagnosis). 2 The purpose of this manuscript is to review the literature regarding the pathophysiology, diagnosis and treatment of immune thrombocytopenia and to provide essential guidelines for students in medicine and young physicians, taking into consideration that few data is available on the management of patients suffering from ITP.

Search Strategy and Selection Criteria

A literature search was computed by two independent investigators using the MEDLINE database, PubMed, and Google Scholar search services with the following key words and word combinations: immune thrombocytopenia, immune thrombocytopenic purpura, ITP, ITP treatment, ITP guidelines, ITP pathophysiology. Inclusion criteria incorporated relevant articles in English, published in between 1st January 2004 and 1st August 2016, that addressed ITP as their main theme (pathophysiology, diagnosis and treatment). The educational program as well as congress abstracts of the European Hematology Association and ITP working group were also consulted for inclusion in this manuscript. The exclusion criteria were case reports, unavailability of any full article, unclear presentation, non-relevant studies and reports of different languages other than English. The common features were assembled into this present review.

Pathophysiology

Although the pathophysiology of the primary ITP is still unclear, the disease is characterized by an antibody mediated destruction of platelets and a suppression of megakaryocyte and platelet production on the basis of immune deregulation. [3, 4] Both genetic and environmental factors are involved in the production of autoantibodies. A predisposition to autoimmunity, induced by genetic factors, exists and is associated with environmental factors (infection, inflammation, mimicry) which trigger an immune response represented by activated B cells, shifted Th1/Th2 balance, and increased phagocytic activity. Platelet-specific autoantibodies are directed against GPIIb/IIIa (which contains important B-cell and T-cell determinants and seven immunodominant epitopes), GP Ib/IX or other platelet glycoproteins. [4] Antiplatelet antibodies mediate the accelerated clearance from the circulation through the mononuclear phagocytic system. Cellular immunity is disturbed, T-cell and cytokine profiles are shifted towards a Th1/Th2, Tc1/Tc2 and Th17 pro-inflammatory immune response and a reduction in suppressor T-regulatory cells is involved. [3]

The pathophysiology of secondary immune thrombocytopenia, more complex than the one of the primary immune thrombocytopenia, is cause dependent. In chronic infection with Heli-

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[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania.

Correspondence:
Mihnea-Alexandru Găman
Email: mihneagaman@yahoo.com

cobacter pylori, immune thrombocytopenia is the result of antiplatelet autoantibodies produced by molecular mimicry to H. pylori antigens such as CagA, which induce platelet aggregation and platelet expresion of p-selectin and phosphatidylserine by some strains of H. pylori, associated with susceptibility to the infection of the human host (variation in Lewis antigens at the host mucosal surface, variation in the patient's individual HLA) and an increased phagocytic activity of monocytes and decreased FcγRIIb. Hepatitis C virus (HCV) and human immune deficiency virus (HIV) can provoke anti-HCV and anti-HIV autoantibodies respectively that cross-react with platelet glycoproteins and form immune complexes. [3] Acute infections (Epstein Barr virus, varicella zoster virus, influenza virus) or vaccination induce immune thrombocytopenia by molecular mimicry and/or immune stimulation by specific antigen exposures that tip the immune response to break tolerance to platelets in susceptible persons. [3]

Autoimmune disorders, such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome and rheumatoid arthritis are associated with immune thrombocytopenia are characterized by immune deregulation such as the shift in Th1/Th2 balance, increased Th17, and altered T-cells regulatory profiles. Immune thrombocytopenia from SLE is determined by the anti-GPIIb/IIa antibody-mediated platelet destruction and by the inhibition of megakaryopoiesis by antibodies directed against the thrombopoietin receptor (CD110, cluster of differentiation 110). [5] Primary ITP is also a hematological feature of an auto-immune condition entitled antiphospholid syndrome, in which patients are at risk of developing arterial or venous thrombosis, as seen in a systematic review and meta-analysis conducted by Moulis et al. An association (strong if lupus anticoagulant was present, and weaker, but still present, if anticardiolipin antibodies were found) between the presence of antiphospholipid antibodies and the occurrence of arterial or venous thrombosis. [6]

Some authors also believe that oxidative stress can be involved in the development of ITP, since reactive oxygen species that are excessively produced attack fundamental components of the cell such as proteins, which are highly immunogenic and may induce autoantibody production. [7, 8] In small group of 24 patients, external administration of antioxidants via antioxidant supplements and a healthy diet improved therapeutic response and patient evolution. [9]

Diagnosis

The first step in the diagnosis of immune thrombocytopenia is performing a blood marrow smear to confirm the low platelet count. If platelet aggregation is shown, a different anticoagulant (EDTA versus citrate) must be used to rule out the possibility of a false thrombocytopenia, a frequent clinical situation in practice. The diagnosis of immune thrombocytopenia is one of exclusion and is based on the patient's history, physical examination, complete blood count and examination of the peripheral blood smear. 10 The evaluation of ITP requires a basic evaluation and additional tests of potential value. The basic evaluation is represented by: patient, family and medication history, physical examination, complete blood count, peripheral blood film, quantitative immunoglobulins, bone marrow examination (in patients › 60 years old, those with systemic symptoms or when splenectomy is considered), blood group (Rh), H. pylori, HCV, and HIV tests. Additional tests which may have a potential value are represented by: antiphospholipid antibodies (Ig G and Ig M anti β2 GPI antibodies, Ig G and Ig M anti-cardiolipin antibodies), circulate lupus anticoagulant, thyroid stimulating hormone (TSH), antithyroid antibodies, antinuclear antibodies, anti-DNA antibodies, pregnancy test in women of childbearing years, polymerase chain reaction for parvovirus and cytomegalovirus (CMV). The determination of thrombopoietin, reticulated platelets, platelet associated immunoglobulin G, bleeding time, serum complement, platelet survival study have unproven benefits. Tests to rule out an important hematological emergency, disseminated intravascular coagulation, must be performed: prothrombin time, Kaolin time, fibrinogen, and platelet count.

The Treatment of Primary Immune Thrombocytopenia

Treatment is indicated in adult patients with platelet counts below 20.000-30.000/mm3, with bleedings or bleeding risk, trauma, surgery, anticoagulant therapy or patients whose profession/lifestyle predisposes to trauma. Therapy is used to increase the platelet count to a safe level (50.000/mm3) and to prevent further bleeding with minimal toxicities. Most immune thrombocytopenic therapies suppress the active B-cells, T-cell and the mononuclear phagocytic system, and are likely to lead to the downregulation of inflammation and tipping of immune balance back towards tolerance. [3] The latest recommendations of the Immune Thrombocytopenia International Working Group consensus for ITP treatment are presented below.

First line therapy is represented by corticosteroids, intravenous immunoglobulins (IVIg) and intravenous (IV) anti-RhD. Corticosteroids (Dexamethasone 40 mg daily for four days every three weeks, or Methylprednisolone 30 mg/kg/day for seven days, or Prednisone 0.5-2 mg/kg/day for two-four weeks) used in combination with IVIg or IV anti-RhD rapidly increase platelet counts in patients with significant thrombocytopenia (‹5.000/mm3) and extensive bleeding. Corticosteroids globally influence the immune system by suppressing T-cell and B-cell reactivity while inducing tolerogenic patterns in T cells, dendritic cells and circulating cytokines. [3, 11] Toxicities vary with the length of administration, having a lower rate of side effects when a short-term bolus therapy is used (23% of patients have a sustained response at 39 months). [2]

Intravenous immunoglobulins or IVIg (0.4g/kg/day for five days or infusions of 1g/kg/day for one-two days) determined in 65-80% of patients an increase of the platelet count within 24-48 hours. [2, 10, 12] The mechanism of IVIg is unclear, but is thought to tip the immune balance back towards tolerance by inducing inhibitory phenotypes in the mononuclear phagocytic system (FcγRIIb) and possibly by inhibiting complement-mediated cell damage, suppressing B and T cells and exerting a direct anti-idiotype effect on circulating functional antiplatelet autoantibodies. [13] Sustained response is typically for three-four weeks, but may persist for months. Common toxicities are represented by hemolytic anemia, headaches, fever, chills, and infusion reactions. Rare toxicities are: aseptic meningitis, acute renal failure, thrombotic events.

Intravenous anti-D (50-75μg/kg) has a similar dose-dependent

response rate to IVIg in four-five days. IV anti-D modulates FcγRs by blocking phagocytic cells via anti-Rh autoantibodies bound to erythrocytes and may modulate immunity by anti-idiotype activity, Fc receptor modulation, cytokine shifts and downregulation of phagocytosis. Therapy significantly reduced the accelerated clearance of platelets with little effect on the platelet production. [14, 15] Common toxicities are represented by mild hemolytic anemia, headaches, fever. Rare toxicities are: intravascular hemolysis, renal failure, disseminated intravascular coagulation, death. The concomitant use of corticosteroids may enhance the platelet response and reduce the side effects. [16]

Second-line treatment is represented by: splenectomy, inhibition of the monocytic phagocytic system therapy (vinca alkaloid regimens), immunosupressive therapy (Azathioprine, Cyclosporin A, Cyclophosphamide), anabolic steroids (Danazol), anti-CD20 therapy (Rituximab), TPO receptor agonists (Eltrombopag, Romiplostim). Splenectomy remains the treatment option with the highest likelihood of producing cure. It is indicated by some authors as first line therapy in immune thrombocytopenia because the procedure appears to be a curative treatment. It is recommended to wait at least six months from diagnosis before performing splenectomy due to the chance of spontaneous remission. Splenectomy removes a large component of the mononuclear phagocytic system, the site of platelet sequestration, and also a lymphoid organ important for immune function, especially B-cell development and restoration of T-cell variation. [3, 17] Splenectomy is associated with a better response in younger patients with no liver sequestration of platelets, 80% of patients responding to treatment in one to 24 days. Response is sustained with no additional therapy in approximately two-thirds over 5-10 years. The patients requiring splenectomy must be vaccinated before splenectomy with antipneumococcal vaccine and after splenectomy should undergo Streptococcus pneumoniae, Haemophilus influenzae type B and Neisseria meningitidis vaccines to prevent sepsis. The complications of the procedure are: hemorrhage, peripancreatic hematoma, subphrenic abscess, wound infection, pneumococcal infection, and thrombosis. Laparoscopic splenectomy reduced complication rates and is associated with faster recovery, but relapse can occur due to an accessory spleen which may require further surgical intervention. [18, 19]

Anti-CD20 therapy (Rituximab) decreases CD20-expressing B-cells and the shift to tolerance, increases regulatory T-cells, diminishes detectable oligoclonality in T-cell population, stimulates CD110 and increases the platelet number. [17] It is used as the standard lymphoma regimen of 375mg/m2 weekly for four weeks. [20, 21] The optimal dose and frequency of rituximab administration for the treatment of immune thrombocytopenia is still unknown. [22] Sixty percent of patients obtained response (40% complete response) in one to eight weeks. Severe side effects include progressive multifocal leukoencephalopathy and reactivation of hepatitis B. Less serious toxicities include first-infusion reactions such as fever, chills and serum sickness. [16]

Cyclosporine A in dose of 2.5-3 mg/kg/day has immunomodulatory effects, a rate of response of 50-80% in small series and moderate and transient side effects. It increases platelet count alone or in combination with prednisone. Azathioprine has an immunomodulatory effect (40% response rate) and needs to be continued for three to six months. Toxicities have a low incidence and are in general mild. Cyclophosphamide induces response in 25-85% of patients in one to sixteen weeks with a sustained response up to 50%. [2]

Danazol and Dapsone are corticosteroid-sparing agents particularly useful in elder patients and at those to which splenectomy is contraindicated.

Vinca alkaloid regimens have highly variable transient response in 10-75% of patients, with a response-time of five to seven days, an average of ten months sustained response and moderate toxicities: neuropathy, neutropenia, fever, thrombophlebitis or inflammation at the infusion site.

Thrombopoietin (TPO) receptor agonists have provided excellent responses in both splenectomized and non-splenectomized patients. [2] They interact directly with the TPO receptor on megakaryocytes to stimulate platelet production and improve regulatory T-cell activity. [23]

Romiplostim is used in a dose of 1-10 μg/kg both in non-splenectomized or splenectomized patients, with a response time of one to four weeks. It is a competitive inhibitor of TPO and binds directly to the TPO binding site on cMPL.

Eltrombopag is used in a dose of 50 mg or 75 mg daily, with a response-time of 14 days. It may induce hepatotoxicity. Dizziness and reversible introversion have also been reported, but it seems that this TPO receptor agonist gives rise to less frequent and less severe side effects than corticosteroid therapy. [24, 25] Side effects of TPO mimetics are represented by the development of bone marrow reticulin fibrosis, venous thromboembolism, myeloid malignancies, rebound thrombocytopenia, and headache.

The preferred approach on the treatment of secondary ITP is treating the underlying disease. Treatment regimens of ITP in patients failing first and second-line therapy are TPO mimetics and therapy with minimal data, considered to have potential or considerable toxicities: campath-1H (fever, chills, rigor, intracranial hemorrhage, cerebral vein thrombosis, infection, severe intravascular hemolysis, death), combination chemotherapy (risk of secondary malignancies, pancytopenia, hemorrhagic cystitis, neuropathy), hematopoietic stem cell transplantation (myelosuppresion, infection, graft-versus host disease, mucocutaneous bleeding, death).

The treatment of ITP in pregnancy - corticosteroids or IVIg are recommended as first line therapy in the first two trimesters when the patient is symptomatic and if the platelet count falls below 20-30.000/mm3. Splenectomy is rarely indicated in pregnancy, but is the best option in the second trimester if absolutely necessary. [2] In neonates with clinical hemorrhage or platelet counts below 20.000/mm3, therapy with a single dose of IVIg 1g/kg induces a rapid response. Rituximab, vinca alkaloids, danazol, TPO-mimetics should be avoided in pregnancy due to teratogenicity.

The emergency therapy requires a high-dose of intravenous corticosteroids and IVIg or, as alternative, platelet transfusion with or without IVIg, vinca alkaloids, emergency splenectomy and anti-fibrinolytics.

Conclusions

The current manuscript reviews the therapeutic guidelines recommended by international experts in patients with immune thrombocytopenia in order to improve treatment outcome as data regarding the management of such patients is relatively scarce. However, there are studies in the medical literature that report several degrees of inappropriateness in how these guidelines are put into practice as, in some cases, recommendations do not always address all the therapeutical obstacles that the clinician encounters when diagnosing and treating patients with ITP. [26]

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