EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 8
574-579
Year: 2022

IMMUNE THROMBOCYTOPENIA (ITP): A REVIEW ON PATHOGENESIS AND TREATMENT ADVANCEMENTS

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Article Received on 12/06/2022 **Article Revised on 01/07/2022** **Article Accepted on 31/07/2022**

ABSTRACT
Immune thrombocytopenia (ITP) is an immune-mediated bleeding disorder characterized by the destruction of platelets and megakaryocytes in the spleen and bone marrow respectively, by pathogenic autoantibodies and/or autoreactive T cells. This review discusses the pathophysiology of ITP and the different treatment modalities which are in current use.

KEYWORDS: immune thrombocytopenia, platelets, bleeding disorder, autoantibodies, treatment.

INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired, complex bleeding disorder where autoimmune antibodies and/or T cell-mediated response against platelets and megakaryocytes (MK) cause peripheral platelet destruction and bone marrow MK loss, resulting in decreased platelet counts and their impaired production.[1] When peripheral platelet count falls below 100 x 10^9/L in the absence of other platelet-lowering factors, it is rendered as primary ITP.[2] Primary ITP constitutes 80% of the ITP cases in the adult population[3] but can be observed in children as well. It has a prevalence of around 9-9.5/100,000 adults and an incidence of about 3-3.3/100,000 adults per year.[3,4] Its incidence increases with age[4] with a peak occurring in males older than 75 years.[3] About 20% of adults are affected by secondary ITP[4], comprising all types of immune-mediated thrombocytopenia cases which cannot be labeled as primary.[2] The factors predisposing to secondary ITP can be inherited or acquired[4], and its various associations are listed in Table.1. 'Molecular mimicry' is the etiology behind secondary ITP, where the immune system misinterprets any antigen as a platelet one, giving rise to cross-reactive anti-platelet autoantibodies[4], as seen for platelet glycoprotein IIIa and HIV glycoprotein120 or HCV core envelope 1 protein.[3] ITP is called 'newly-diagnosed' when the duration of symptoms is less than 3 months; 'persistent' when symptoms last for 3 to 12 months, and 'chronic' when symptoms persist beyond 12 months.[4]

Table 1: Conditions associated with secondary ITP.

Drug-induced[2]
Hematological malignancies[3]
Systemic autoimmune diseases Systemic lupus erythematosus[3] Rheumatoid arthritis[4]

Chronic viral infections Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Hepatitis C virus (HCV), Human Immunodeficiency Virus (HIV), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)[3], Helicobacter pylori[4] Primary immune deficiencies[3]

Primary ITP causes isolated thrombocytopenia[1], increasing the risk of bleeding events.[2] Patients can clinically present with bruising or petechiae, purpura, and mucosal bleeding in the urinary or gastrointestinal tracts.[1,4] However, bleeding symptoms may not always be present.[2,5] Therefore, the term "Immune thrombocytopenia" was coined to replace the previously-used terminology of "Idiopathic thrombocytopenic purpura".[5] The risk of major bleeding and associated mortality increase with increasing age.[2]

Pathogenic Mechanisms of ITP

ITP is associated with complex and multidimensional pathophysiological mechanisms[1] and its primary triggering factors are unclear.[3] It is presumed that the breakdown of immune tolerance leads to a cascade of events involving both innate and adaptive immune systems, resulting in ITP.[3] Both humoral and cell-mediated responses are involved.[4]

1). Production of antiplatelet autoantibodies by plasma cells

It has long been known that the formation of a humoral factor is a major trigger for ITP onset.[6] A primary disturbance in the regulatory T-cell function triggers the splenic follicular helper T-cells, subsequently stimulating the differentiation of splenic B cells into autoimmune plasma cells which produce antiplatelet antibodies including IgM and IgG[3] (IgG1 in 77% of the observed cases).[7] IgA antibodies are also detected.[8] These antiplatelet antibodies attack several platelet glycoprotein (GP) antigens[3], notably GPIIb/IIIa (fibrinogen receptor), GPIb/IX (von Willebrand factor) and less frequently GPIa/IIa (collagen receptor) and GPIV.[9] The tagged platelets are then removed from the peripheral circulation through several pathways which are discussed below.

i). Complement-dependent cytotoxicity

Platelet-autoantibody complexes lead to the activation of the classical complement pathway.[3] This mechanism destroys the targeted platelets by the formation of the membrane attack complex (MAC).[10] Anti-GPIIb/IIIa antibodies are more likely to activate complement pathways than anti-GPIb/IX.[11] Both splenic and hepatic monocytes and macrophages have Fc gamma receptors (FcγR) and complement receptor 1, through which they bind to the complement fraction C3b of the MAC, leading to the phagocytosis of the opsonized platelets.[3,8,12]

v). FcγR-independent pathway

Platelet destruction also takes place by a FcγR-independent pathway which involves platelet desialylation (release of sialidase), favoring their binding to the hepatic Ashwell-Morell receptor and subsequent clearance.[3,8]

2. T-cell mediated autoimmunity

i). CD4+ T cell-mediated autoimmune mechanisms

A skewing towards higher levels of CD4+ T-cell types (Th1, Th17, Th22, and splenic follicular helper cells) along with increased levels of CD4+ T-cell cytokines (IL-2, IL-10, IFN-γ) have been implicated in ITP pathogenesis, which stimulates B-cell differentiation into antibody-secreting plasma cells.[8] The presence of autoreactive CD4+ T-cells that target platelet GPIIb/IIIa antigens has also been found.[13]

ii). CD8+ T cell-mediated autoimmune mechanisms

Increased levels of CD8+ T-cells can be found in some ITP patients even in the absence of autoantibodies.[8] CD8+ T-cells can directly kill platelets and induce apoptosis.[14]

iii). Regulatory T-cell dysfunction

Regulatory T-cells play a pivotal role in checking the autoimmunity and help maintain immune tolerance.[8] ITP patients have a reduction in the number and function of regulatory T-cells, indicating a loss of immune tolerance.[15]

2). Impaired megakaryocyte function

Almost two-thirds of ITP patients have autoantibodies that inhibit MK maturation from CD34+ hematopoietic progenitor cells.[16] CD8+ T-cells can cause impaired MK maturation and thrombopoiesis even when thrombopoietin levels are normal.[4,17] In some cases, low thrombopoietin levels and complement-dependent cytotoxicity against MKs result in deficient megakaryopoiesis and thrombopoiesis, respectively.[3] CD8+ T-cells can inhibit platelet production also by inhibiting MK apoptosis.[18]

Treatment Strategies for ITP

The goal of ITP treatment is not to achieve a normal physiological platelet count, but to attain a level where optimum hemostasis is maintained. As primary and secondary ITP have clinically distinct etiologies, their treatments differ. Secondary ITP usually has a better prognosis because the treatment of the associated underlying disorder leads to restored platelet count and decreased autoantibody titers.[2,4] According to the current guidelines, the treatment should be initiated if

bleeding symptoms are present.[19,20] Treatment decisions based on platelet count threshold remain controversial.[2] However, platelet levels lower than 30 $x10^9$/L may cause fatal bleeding.[21]

Several treatment modalities are being utilized, which target various aspects of ITP pathophysiology.

a). First-line Treatments

The goal of first-line treatments is to reduce platelet degradation and clearance by inhibiting autoantibody production.[1,4] Most patients with primary ITP relapse if first-line treatment is discontinued.[22]

i). Corticosteroids are the first-line treatment for ITP.[1,4,23] Oral prednisolone, IV methylprednisolone, or oral dexamethasone are used. High doses of steroids should be used for a short period as the side effects of the treatment occur considerably.[24]

ii). Intravenous immunoglobulin (IVIG) is used in cases when steroids are contraindicated or if the platelet level falls on tapering steroids.[4,24]

iii). Anti-D is especially useful for children and HIV-associated ITP, but should not be used in patients with anemia or evidence of hemolysis.[24]

b). Second-line Treatments

i). Immunosuppressive agents such as Rituximab (anti-CD20 antibody) suppress the autoimmune mechanisms.[1] Only 50 to 60% of patients respond to rituximab, but long-term remission is observed in approximately 30% of patients who show an initial response.[24]

ii). Thrombopoietin receptor agonists (TPO-RA) such as Romiplostim and Eltrombopag are effective, especially for refractory ITP.[1] They increase platelet production and levels by activating thrombopoietin receptors on MKs.[4] Increased bone marrow MK numbers and decreased serum antiplatelet antibody levels are also seen, suggestive of immunomodulation.[1] Approximately 30% of treated cases demonstrate sustained elevated platelet counts after drug tapering.[1] Romiplostim attenuates the autoimmune response by improving the regulatory T-cell activity.[25] Eltrombopag shifts the monocyte-FcγR balance toward the inhibitory FcγRIIb. Decreased monocyte/macrophage-mediated phagocytosis has also been observed with in vitro use of Eltrombopag.[26]

iii). Mycophenolate mofetil (MMF) works against autoreactive T and B cells, and has response rates of 50 to 80%.[23] It is effective, especially against refractory and glucocorticoid-resistant ITP.[24]

iv). Azathioprine is safely used for pregnant females with ITP, in contrast to MMF.[24]

v). Splenectomy provides a long-term response when the patient cannot tolerate or afford medical treatments.[1,2] Patients require post-splenectomy care including continued penicillin prophylaxis and regular vaccination against encapsulated organisms.[24]

Infection-related morbidity and mortality have been reduced owing to the use of IVIG, IV Anti-D, rituximab, and TPO-RAs over steroids and splenectomy. Dapsone, danazol, vincristine, and hydroxychloroquine have also been used with limited success.[24] Immunosuppressive agents used for ITP other than rituximab include cyclophosphamide[27], rapamycin[28] and anti-TNF agents.[29]

c). Third-line Treatments/Combination regimes

Refractory ITP can be treated with combined regimes.[24] According to a multicentric FLIGHT trial conducted in the United Kingdom, the combination of MMF with a glucocorticoid proves to be an effective first-line treatment for ITP, as compared to a glucocorticoid-only regimen.[23] Immunosuppressive agents can be combined with TPO-RAs.[30]

d). Newer therapeutic advances

Trials for new therapeutic strategies for ITP are underway, which can potentially modify the management of this disease in the near future. Some of the new advancements include:

i). Novel TPO-RAs – Avatrombopag, 23A11 and amifostine.[24]

ii). FcR binding and signaling inhibitors – GMA161.[31]

iii). T cell co-stimulation targeting agents – Toralizumab (IDEC-151)[32] and Ruplizumab (hu5c8).[33]

iv). Spleen tyrosine kinase inhibitor – Fostamatinib.[34]

v). Low-dose histone deacetylase inhibitor – Chidamide. This drug alleviated thrombocytopenia in passive and active ITP murine models, attenuated phagocytosis of antibody-coated platelets, promoted the peripheral conversion of T cells into Treg cells and restored Treg cell suppression in vivo and in vitro.[35]

vi). All-trans retinoic acid — Low-dose rituximab combination – This regimen significantly increased the overall and sustained response in steroid-resistant or relapsed adult ITP.[36]

COVID-19 and ITP

Multiple cases of ITP secondary to moderate-to-severe COVID-19 have been reported.[37,38,39] COVID-19-associated ITP can arise due to the underlying systemic immune dysregulation and including molecular mimicry. Severe life-threatening bleeding has not been reported. Patients have shown a good response to short courses of glucocorticoids and IVIGs.[5]

Abbreviations
FcγR: Fc gamma receptors
GP: Glycoprotein
HCV: Hepatitis C virus
HIV: Human Immunodeficiency Virus
ITP: Immune thrombocytopenia
IVIG: Intravenous immunoglobulin
MAC: Membrane attack complex
MK: Megakaryocyte
MMF: Mycophenolate mofetil
TNF: Tumor necrosis factor
TPO-RA: Thrombopoietin receptor agonist

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