



**Measurement of Immunoglobulin A and
Immunoglobulin M and their relation to
treatment outcome of Immune
Thrombocytopenic Purpura**

Thesis

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Medicine*

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قالوا

لَسْبَحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Abbreviations

AMR	Ashwell-Morrell receptor
APCS.....	Antigen presenting cells
ASH.....	American society of hematology
Breg.....	Regulatory B-cell
C.....	Constant region
CDRs.....	Complementarity determining regions
CH.....	Constant heavy chain
CL	Constant light chain
CVID.....	Common variable immunodeficiency
DCs	Dendritic cells
FcYR.....	Fcy receptor
Foxp3	Transcription factor forkhead box protein 3
FRs	Framework regions
G6PD.....	Glucose 6-phosphatase deficiency
GP	Platelet surface glycoprotein
HDD	High dose dexamethasone
IBLS	ITP bleeding scale
ICH.....	Intracranial hemorrhage
IFN	Interferon
Ig	Immunoglobulin
IL.....	Interleukin
ITP.....	Idiopathic or immune thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
IWG.....	International ITP working group
JAK 2	Janus kinase 2
MALT	Mucosal associated lymphoid tissue

List of Abbreviations

mIgM.....	Membrane bound IgM
MMF	Mycofenolate mofetil
Mrna.....	Messenger ribonucleotide analogue
OPSS`	Overwhelming postsplenectomy sepsis
RNA	Ribonucleotide analogue
sIgA.....	Secretory IgA
sIgM	Ecreted IgM
STAT 3.....	Signal transducer and activator of transcription 3
TGF	Tumor growth factor
Th	T helper
TPO	Thrombopoietin
TPO-RAs.....	Thrombopoietin receptor agonist
Treg	Regulatory T cell
V	Variable region
Vas	Vinca alkaloids
VH.....	Variable heavy chain
VL	Variable light chain
VTE.....	Venous thromboembolism

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Abstract

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura, is defined as isolated thrombocytopenia with normal bone marrow and in the absence of other causes of thrombocytopenia. ITP has two distinct clinical syndromes, manifesting as an acute condition in children and a chronic condition in adults. ITP is primarily a disease of accelerated platelet destruction and impaired platelet production. Auto antibodies against platelet surface glycoproteins (GP), such as GPIIb/IIIa and GPIb/IX complexes, play major roles in both platelet destruction and impaired platelet production. Immune dysregulation, as represented by elevated or decreased serum immunoglobulin (Ig) levels, may increase disease severity as represented by failure to respond to treatment. These alterations in Ig levels may represent an inflammatory or activated immune state that makes the disease more difficult to control with specific treatment. Patient with common variable immunodeficiency (CVID) with low IgG, IgA, and/or IgM levels have 22% incidence of autoimmune disease, such as ITP, supporting the association of abnormal Ig levels with ITP.

Aim of the work: To measure the level of Immunoglobulin M (Ig M) and Immunoglobulin A (Ig A) and their relation to the treatment response in patients with immune thrombocytopenic purpura (ITP).

Methods: The study was conducted upon 60 ITP adult patients who were divided into 2 groups: group I were responder to the standard treatment (steroids), group II were non responder to the standard treatment. IgM and IgA were measured by Enzyme Linked Immunosorbent assay (ELISA).

Results: In this study the median level of IgA was high in non-responder compared to those who were responder to the treatment (group I) and the control group. Median level of IgM was low in non-responder compared to responder patients and to control group.

Conclusion: We concluded that statistically significant difference between responder and non-responder ITP patients as regard the level of IgM as the patients who had IgM level below the median were more resistant to steroid which is the standard treatment in ITP. On the other hand there was no significant difference in the level of IgA between responder and non-responder ITP patients.

Key word: Immunoglobulin M, Purpura, Immunoglobulin A

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura, is defined as isolated thrombocytopenia with normal bone marrow and in the absence of other causes of thrombocytopenia. ITP has two distinct clinical syndromes, manifesting as an acute condition in children and a chronic condition in adults (*Salib et al., 2016*).

ITP is primarily a disease of accelerated platelet destruction and impaired platelet production. Auto antibodies against platelet surface glycoproteins (GP), such as GPIIb/IIIa and GPIb/IX complexes, play major roles in both platelet destruction and impaired platelet production (*Noroozi et al., 2015*).

Acute ITP often follows an acute infection and has a spontaneous resolution within 2 months. Chronic ITP persists longer than 6 months without a specific cause (*Neunert et al., 2011*).

The diagnosis of ITP is a process of exclusion. First, it has to be determined that there are no blood abnormalities other than a low platelet count, and no physical signs other than bleeding. Then, secondary causes (5–10 percent of suspected ITP cases) should be excluded. Such secondary causes include leukemia, medications (e.g., quinine, heparin), lupus erythematosus, cirrhosis, HIV, hepatitis C,

congenital causes, Antiphospholipid syndrome, von Willebrand factor deficiency and others (*Najaoui et al., 2012*).

Although corticosteroids and splenectomy remain the main lines of ITP treatment, a new class of drugs, i.e., thrombopoietin receptor agonists (TPO-RAs) and rituximab, have substantially broadened the therapeutic options for refractory ITP patients. Moreover, the success of TPO-RAs in ITP patients shows that reduced platelet production caused by impaired megakaryocytopoiesis plays a greater role in ITP than previously recognized (*Liu et al., 2011*).

Immune dysregulation, as represented by elevated or decreased serum immunoglobulin (Ig) levels, may increase disease severity as represented by failure to respond to treatment. These alterations in Ig levels may represent an inflammatory or activated immune state that makes the disease more difficult to control with specific treatment (*Bussel et al., 2009*).

Certain patient populations with known immunologic disorders have an increased the risk of ITP; supporting the concept that immune dysregulation may contribute to the development of ITP (*wang et al., 2005*).

Patient with common variable immunodeficiency (CVID) with low IgG, IgA, and/or IgM levels have 22% incidence of autoimmune disease, such as ITP, supporting

the association of abnormal Ig levels with ITP (*Wang et al., 2005*).

IgA deficiency is also related to ITP in perhaps 1% to 2% of cases of ITP, but this may be primarily in those cases with concomitant IgG subclass deficiency (*Schulze et al., 2011*).

Elevation in IgA may represent aberrations in mucosal immunity, leading to systemic autoimmune effects. The clear relation between *Helicobacter pylori* infection and immune thrombocytopenia suggests a possible association between mucosal inflammation and immune mediated destruction of platelets (*Liebman et al., 2009*).