

Assessment of Interleukin-27 in Patients with Primary Immune Thrombocytopenia

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدقة الله العظيم

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List of Abbreviations

Abb.	Meaning
ADCC	Antibody-dependent cell-mediated cytotoxicity
AHR	Aryl hydrocarbon receptor
ALPS	Autoimmune lymphoproliferative syndrome
AML	Acute myeloid leukemia
ANOVA	One Way Analysis of Variance
AP-1	Activator protein 1
APC	An antigen-presenting cell
APCs	Ab-platelet complexes
AUC	Area under the curve
Avidin-HRP	avidin-horseradish peroxidase
CCL5	Chemokine (C-C motif) ligand 5
CLF	Cytokine-like factor 1
C-Maf	Musculoaponeurotic fibrosarcoma proto-oncogene
COX-2	Cyclooxygenase-2
CpG	Cytosine, Guanine triphosphate deoxynucleotides with phosphodiester link inbetween
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T-lymphocyte antigen-4
CVID	Common variable immunodeficiency
CXCR3	CXC chemokine receptor
DCs	Dendritic cells

List of Abbreviations (Cont.)

Abb.	Meaning
DSS	Dextran sodium sulfate
EAE.....	Experimental autoimmune encephalomyelitis
EAU	Experimental Autoimmune Uveitis
EBI3	Epstein-Barr virus–induced gene 3
Gp	Glycoprotein
EMT	Epithelial–mesenchymal transition
FOXP3	(Forkhead box P3) a master regulator of the regulatory pathway in the development and function of regulatory T cells
IBD.....	Inflammatory bowel disease
ICOS	Inducible costimulator
IFN γ	Interferon gamma
IL.....	Interleukin
IRF	Interferon regulatory factor
IRGs	Interferon-Regulated Genes
ITP	Idiopathic (immune) thrombocytopenic purpura
IVIG	Intravenous Immunoglobulin
JAK	Janus kinase
LPS.....	Lipopolysaccharides
MAPK.....	Mitogen-Activated Protein Kinases signaling
MHC	Major Histocompatibility complex

List of Abbreviations (Cont.)

Abb.	Meaning
MMP	Matrix metalloproteinase
NK.....	Natural killer
NPV	Negative predictive value.
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PGE2	Prostaglandin E2
PPV	Positive predictive value
PRRs	Pattern recognition receptors
R.....	Receptor
RES	Reticuloendothelial system
ROR γ	Retinoic acid receptorRAR-related orphan receptor gamma
SLE	Systemic lupus erythematosus
SNPs.....	Single nucleotide polymorphisms
SOCS	Suppressors of cytokine signaling
STAT	Signal transducer and activator of transcription factor
TAR.....	Thrombocytopenia-absent radius
T-bet	T-box protein expressed in T cells
TFH.....	Follicular helper T cells
TGF- β	Transforming growth factor beta

List of Abbreviations (Cont.)

Abb.	Meaning
Th	Helper T
Tim-3	T-cell immunoglobulin and mucin domain-3
TLRs	Toll-like receptors
TNBS	2,4,6-trinitrobenzenesulfonic acid
TNF α	Tumor necrosis factor alpha
TNF β 1	Tumor necrosis factor-beta related
TPO	Thrombopoietin
Tr1	Type 1 regulatory T cells
TRAIL	Tumor necrosis factor–related apoptosis-inducing ligand
Treg	Regulatory T
VEGF	Vascular endothelial growth factor

INTRODUCTION

*A*utoimmune diseases result from complex interactions among different immune cell types, including both T and B lymphocytes and professional antigen-presenting cells, such as macrophages and dendritic cells. These cellular interactions result in auto-aggressive responses that target a number of different cell types in different tissues and organs in a relatively large number of autoimmune disorders. Although the etiology of most autoimmune diseases is unknown, recent years have witnessed important advances in our understanding of how the different immune cell types involved in autoimmunity communicate with one another, how they trigger autoimmune inflammation and how they cause tissue damage. As key elements of this communication network, cytokines and chemokines orchestrate the recruitment, survival, expansion, effector function and contraction of autoreactive lymphocytes in autoimmunity (*Santamaria, 2001*).

Primary immune thrombocytopenia (ITP) is an autoimmune disorder with a significant incidence of about 3.3 per 100,000 adults/year (*Terrell et al., 2010*). ITP is rarely fatal. However, in many adults treatment is unsatisfactory, with as much morbidity from treatment immunosuppressive effects as from bleeding (*Cooper and Bussel, 2006*).

Interleukin-27 (IL-27) is a cytokine with both pro-inflammatory and anti-inflammatory effects. There is accumulating evidence suggesting various roles of IL-27 in autoimmune diseases in human's e.g. rheumatoid arthritis, Crohn's disease, psoriasis and multiple sclerosis (***Bosmann and Ward, 2013***).

However, the role of IL-27 in ITP has not been fully elucidated and is still controversial.

AIM OF THE WORK

*A*ssessment of serum level of IL 27 in ITP patients in comparison to healthy controls to evaluate its role in pathogenesis of ITP.

Chapter 1

IDIOPATHIC THROMBOCYTOPENIC PURPURA

Idiopathic (immune) thrombocytopenic purpura (ITP) is a common autoimmune disorder resulting in isolated thrombocytopenia with normal bone marrow and the absence of other causes of thrombocytopenia (figure 1). Approximately 80% of patients present with primary ITP, and 20% can be identified as secondary ITP (*Johnsen, 2012*).

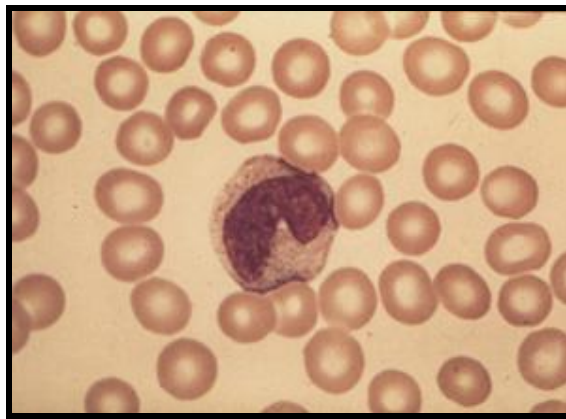


Figure (1): Peripheral blood smear from a patient with immune thrombocytopenic purpura (ITP) shows a decreased number of platelets, a normally-appearing neutrophil, and normally-appearing erythrocytes. ITP is diagnosed by excluding other diseases; therefore, the absence of other findings from the peripheral smear is at least as important as the observed findings. This smear demonstrates the absence of immature leukocytes (as in leukemia) and fragmented erythrocytes (as in thrombotic thrombocytopenic purpura) and no clumps of platelets (as in pseudothrombocytopenia) (*Johnsen, 2012*).