Role of Measurement of Interleukin 10 in Idiopathic (Immune) Thrombocytopenic Purpura -ITP

Thesis

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Candidate

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List of Abbreviations

Abbrev.	Full term
ADP	: Adenosine di-phosphate
AITP	: Autoimmune thrombocytopenic purpura
ALPS	: Autoimmune lymphoproliferative syndrome
APCs	: Antigen presenting cells
cAMP	: Cyclic adenosine mono phosphate
CTL	: Cytotoxic T lymphocytes'
CVID	: Common variable immunodeficiency
DCs	: Dendritic cells
DXM	: Dexamethasone
EBV	: Epstein–Barr virus
GM-CSF	: Granulocyte-macrophage colony stimulating factor
GP	: Glycoproteins
H influenza :	Hemophilus influenzae
HCV	: Hepatitis c virus
HIV	: Human immunodifieciency virus
IgG	: Immunoglobulin G
IL	: Interleukin
IL-10R	: IL-10 receptor
INF	: Interferon
ITP	: Idiopathic thrombocytopenic purpura
IVIG	: Intravenous immunoglobulins
JAK	: Junus kinase
KIR	: Killer cell immunoglobulin-like receptor

LSD : Least Significant Difference
MAPK : mitogen-activated protein kinase
M-CSF : macrophage colony stimulating factor
MHC : Major histocompatibility
NK : Natural killer
NSAIDS : Non-steroidal anti-inflammatory drugs
Os : oxidative stress
PCD : programmed cell death
PDGF : Platelet-derived growth factor
PF4 : Platelet factor 4
RBCs : Red blood cells
RES : Reticuloendothelial system
SD : Standard deviation
STAT : Signal trasducers and activator of transcription
TGF-β : Transforming growth factor beta
Th : T helper cell
TNF-β : Tumor necrosis factor-beta
TPO : Thrombopoietin
Tregs : Regulatory T cells
TXA2 : Thromboxane A2
Tyk : Tyrosin kinase
VEGF : vascular endothelial growth factor
vWF : von Willebrand factor
βTG : β-thromboglobulin

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ABSTRACT

Biological markers useful for defining patient with newly diagnosed pt immune thrombocytopenic purpura (ITP) who are likely to develop the chronic form of the disease are partially lacking. The purpose of this study was to assess the clinical role of cytokines in patient with ITP and correlate its levels with different disease stages.

20 patient with ITP at the onset of their disease, 40 chronic, and 30 healthy matched controls enrolled in this study. Serum levels of IL10 was measured in all patient using quantitative immunoenzymatic assays.

Serum IL10 levels were significantly higher in patients with an acute evolution of ITP than in either healthy controls or patients with chronic ITP.

Conclusion. IL-10 seems to predict the clinical course of ITP, as it is significantly higher at the onset of disease in patients who obtain disease remission in less than 1 year.

Keywords: immune thrombocytopenic purpura, cytokines, IL10 and adult.

Introduction

Idiopathic thrombocytopenic purpura is an acquired disorder characterized by decreased number of circulating platelets known as thrombocytopenia and resulting in subnormal platelet counts.

Epidemiological studies have revealed that the annual incidence of newly diagnosed itp is 4-5\100.000 and that approximately 75 per 100 of cases are of the acute type. ITP is classified by duration into newly diagnosis, persistent (3-12 months) and chronic (more than 12 months) ***(Stevens et al., 2006)***.

Antiplatelet antibodies are responsible for platelet destruction by the reticuloendothelial system and probably for inhibition of megakeryopoiesis. Most cases are considered primary whereas the rest is secondary (attributed to other cause: SLE ,Evan syndrome, HIV and post vaccination). ***(Johnsen, 2012)***.

A normal human platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. Thrombocytopenia refers to a disorder in which there is a relative decrease in platelet count. One common definition of thrombocytopenia that requires emergency treatment is a platelet count below 50,000 per microliter ***(Houghton et al., 2010)***.

Thrombocytopenia symptoms ranging from no symptoms up to excessive bleeding, including nose bleeds and easy bruising according to platelet count. Thrombocytopenia arises from one of three reasons: the bone marrow may not produce enough platelets; too many platelets may be broken down in the blood; or too many platelets may be destroyed in the liver or spleen. Thrombocytopenia can be caused by a variety of conditions or medications***(Furlan et al.,2001).***

Purpura may be caused by spontaneous bleeding under the skin in form of petechiae that may occur on feet and leg and it is painless, round and pinpoint (1 to 3 mm in diameter) petechiae usually appear and fade, ecchymoses. Larger than petechiae, ecchymoses are purple, blue or yellow-green areas of skin that vary in size and shape. They can occur anywhere on the body***(Stasi et al., 2009).***

Idiopathic (immune) thrombocytopenic purpura (ITP) is a heterogeneous clinical disorder characterized by immune-mediated platelet destruction. ITP is usually a benign, self-limiting disease. However, approximately 20% of newly diagnosed ITP progress to a chronic form defined according to standardised criteria ***(Rodeghiero et al.,2009).***

The clinical differences between newly diagnosed and chronic ITP suggest the existence of different patho-physiological mechanisms in two forms humoural and

cellular immunity and inadequate platelet production in the development of this condition ***(Provan et al.,2010).***

Manifests as a bleeding tendency, easy bruising (purpura), or extravasation of blood from capillaries into skin and mucous membranes (petechiae). Although most cases of acute ITP, are mild and self-limited, intracranial hemorrhage may occur when the platelet count drops below 10×10^9/L ($< 10 \times 10^3$/μL); this occurs in 0.5-1% of children, and half of these cases are fatal. ***(Butros et al., 2007)*** Isolated thrombocytopenia in complete blood cell count and peripheral blood smear is the hallmark of ITP. Bone marrow aspiration and biopsy in patients with ITP shows a normal-to-increased number of megakaryocytic in the absence of other significant abnormalities and it also used as a screening for treatment includes corticosteroids In adults older than 60 years, biopsy is used to exclude myelodysplastic syndrome or leukemia ***(Calpin et al., 2006).***

Serum levels of T helper (Th) type 1, Th2 and T-regulatory associated cytokines, such as interferon (IFN) γ, tumour necrosis factor (TNF) α, and interleukin (IL) 2, IL6, IL10, and markers of thrombopoiesis, such as reticulated platelet count and thrombopoietin, were assessed in different phases of ITP in patients and in healthy controls might be considered predictors of ITP progression***(Nugent et al.,2009).***

Interleukin-10 is an important immunoregulatory and an anti-inflammatory cytokine and an inhibitor of IFN-_ synthesis in TH1 cells. Also calledhuman cytokine synthesis inhibitory factor ***(Mocellin et al., 2003)***

IL-10 is secreted by macrophages, TH2cells and mast cells. Cytotoxic T cells also release IL-10 to inhibit viral infection stimulatedNK cell activity. It also functions as an inhibitor of TH1 cells and inhibiting macrophages, it functions as an inhibitor of antigen presentation. Also it can promote the activity of mast cells, B cells and certain T cells.The major immunobiological effect of IL-10 is the regulation of the TH1/TH2 balance. IL-10 is involved in assisting against intestinal parasitic infection, local mucosal infection by costimulating the proliferation and differentiation of B cells. Its indirect effects also include the neutralization of bacterial toxins. It is a stimulator of NK cells, enhances their cytotoxic activity***(Murray.2006)***.Based on its immunoregulatory function, IL-10 and ligands for its receptors are tempting candidates for therapeutic intervention in a wide variety of disease states, including autoimmune disorders, acute and chronic inflammatory diseases, cancer, infectious disease, psoriasis and allergic disease.

Modest but significant improvement has been observed in patients with chronic immune disorders after