Interleukin-33 in Immune Thrombocytopenia: Relation to Disease Severity and Prognosis

Thesis

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Ahmed Said

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List of Abbreviations

Abb.	Full term

Ab ..... *Antibodies*
ADHD ..... *Attention deficit hyperactivity disorder*
A-IPF ..... *Absolute immature platelet fraction*
ALPS ..... *Autoimmune lymphoproliferative syndrome*
AMI ..... *Acute Myocardial Infarction*
ANA ..... *Antinuclear antibody*
ANOVA ..... *Analysis of Variance*
Anti-D ..... *Anti rhesus antibodies*
Anti-Rh ..... *Anti rhesus antibodies*
Apoe ..... *Apolipoprotein E*
ATP ..... *Adenosine triphosphate*
BM ..... *Bone marrow*
BMI ..... *Body mass index*
Ca ..... *Calcium*
CBC ..... *Complete blood count*
CD ..... *Crohn's disease*
CLL ..... *Chronic lymphocytic leukemia*
CMV ..... *Cytomegalovirus*
CNS ..... *Central nervous system*
COPD ..... *Chronic obstructive pulmonary disease*
CR ..... *Complete response*
CV ..... *Cardiovascular*
CVID ..... *Common variable immunodeficiency*
CyA ..... *Cyclosporin A*
D ..... *Rhesus factor*
DAMPs ..... *Damage-associated molecular patterns*
DCs ..... *Dendritic cells*
DIC ..... *Disseminated intravascular coagulation*
DNA ..... *Deoxyribonucleic acid*

List of Abbreviations (Cont...)

Abb.	Full term
DSS	*Dextran sodium sulfate*
DTaP	*Diphtheria–tetanus–acellular pertussis vaccine*
DVT	*Deep venous thrombosis*
ELISA	*Enzyme linked immunosorbent assay*
ER	*Emergency room*
ERK	*Extracellular signal-regulated kinase*
F/U	*Follow up*
FALC	*Fat-Associated Lymphoid Cluster*
g	*Gram*
G0	*Gap zero period in cell cycle*
G1	*Gap 1 period in cell cycle*
G6PD	*Glucose-6-phosphate dehydrogenase*
GI	*Gastrointestinal*
GTPase	*Guanosine triphosphatase*
GYN	*Gynecological*
H pylori	*Helicobacter pylori*
h	*Human tissues*
HCV	*Hepatitis c virus*
Hep C	*Hepatitis C*
HEV	*High endothelial venules*
HF	*Heart failure*
HIV	*Human immunodeficiency virus*
hr	*hour*
Hx	*Skin*
IBD	*Inflammatory bowel diseases*
IBLS	*Immune thrombocytopenia Bleeding Scale*
ICH	*Intracranial hemorrhage*
IgG	*Gamma immunoglobulin*
IL-1	*Interleukin-1*
IL-10	*Interleukin-10*

List of Abbreviations (Cont...)

Abb.	Full term
IL-18	*Interleukin-18*
IL-1RAcP	*Interleukin-1 receptor accessory protein*
IL-1α	*Interleukin-1 alpha*
IL-1β	*Interleukin-1 Beta*
IL-33	*Interleukin-33*
IL-4	*Interleukin-4*
ILC2s	*Type 2 innate lymphoid cells*
IQR	*Enter quartile range*
IRAK-1	*Interleukin receptor associated kinase 1*
ITP	*Immune thrombocytopenia*
IVIg	*Intravenous immunoglobulin*
IWG	*International Working Group*
JAK-STAT	*Janus kinase/Signal Transducer and Activator of Transcription*
JNK	*JUN N-terminal kinase*
KC	*Chemokine*
kg	*Kilogram*
L	*Liter*
M	*Macrophages*
m	*Mouse tissues*
MAPK	*Mitogen-activated protein kinase*
MC	*Mast cells*
MD	*Age-related macular degeneration*
mg	*Milligram*
ml	*milliliter*
MMF	*Mycophenolate mofetil*
MMR	*Measles–mumps–rubella vaccine*
mRNA	*Messenger ribonucleic acid*
MS	*Multiple sclerosis*

List of Abbreviations (Cont...)

Abb.	Full term
MyD88	*Myeloid differentiation primary-response protein 88*
N	*Neutrophils*
NF- κB	*Nuclear factor-κB*
NFAT	*Nuclear factor of activated T cells*
nm	*Nanomolar*
NMR	*Nuclear magnetic resonance*
NR	*No response*
P	*Phosphorylation*
p	*Probability value*
PCR	*Polymerase chain reaction*
PE	*Oral*
Pg	*Picogram*
PGE2	*Prostaglandin E2*
PO	*Per oral*
PR	*Partial response*
R	*Response*
RA	*Rheumatoid arthritis*
RAF	*Rapidly accelerated fibrosarcoma kinase*
RAS	*Rat sarcoma GTPase*
Rh	*Rhesus factor*
RhIG	*Rhesus immunoglobulin*
rhTPO	*Recombinant human thrombopoietin*
SD	*Standard deviation*
SF	*Synovial fluid*
SHC	*Src homology collagen protein*
SIGIRR	*Single Ig IL-1R-related molecule*
SLE	*Systemic lupus erythematosus*
SPSS	*Statistical Program for Social Science version*

List of Abbreviations (Cont...)

Abb.	Full term
sST2	*Soluble receptor suppression of tumorigenicity 2*
ST2	*Receptor suppression of tumorigenicity*
Th	*T-helper*
Th1	*T-helper type 1*
TH17	*T-helper type 17*
Th2	*T-helper type 2*
TLR	*Toll like receptor*
TNBS	*Trinitrobenzene sulfonic acid*
TNF-α	*Tumor necrosis factor alpha*
TPO	*Thrombopoietin*
TPO-RAs	*Thrombopoietin receptor agonists*
TRAs	*Thrombopoietin receptor agonists*
Tregs	*T regulatory cells*
TSH	*Thyroid stimulating hormone*
U	*Urinary*
UC	*Ulcerative colitis*
USA	*United State of America*
VEGF	*Vascular endothelial growth factor*
WBC	*White blood cell*
X^2	*Chi-square*
μL	*Microliters*

Abstract

Background: The pathogenesis of thrombocytopenia in immune thrombocytopenia (ITP) has shifted from the traditional view of increased platelet destruction mediated by autoantibodies to more complex mechanisms where both impaired platelet production and T-cell-mediated effects play a role. Interleukin-33 (IL-33) is a newly identified cytokine of the IL-1 family. There is increasing evidence to suggest that IL-33 is a key inflammatory mediator in a complex network of immune cells and non-immune cells. IL-33 signals via its ST2 receptor and is involved in several autoimmune diseases by regulating T cell immune responses. **Aim:** To assess the level of IL-33 in children and adolescents with ITP and correlate it with disease severity, treatment response and outcome. **Methods:** Fifty young patients with ITP were compared with 40 age- and sex-matched healthy controls. Patients were studied stressing on bleeding manifestations, organomegaly/lymphadenopathy and therapy. Bleeding score was calculated to each patient according to the ITP Bleeding Scale (IBLS). The studied ITP Patients were further classified into 3 subgroups: "newly diagnosed ITP" (ITP within 3 months from diagnosis), "persistent ITP" (ongoing ITP between 3 and 12 months from diagnosis), and "chronic ITP" (ITP lasting more than 12 months). ITP Patients were also classified into active ITP defined as platelet count below 100 x 109/L accompanying with or without bleeding episode or complete response (CR) which was defined as any platelet count of at least 100 × 109/L and absence of bleeding. **Results:** IL-33 levels were significantly lower in ITP patients than controls (median [IQR], 150 [100 – 230] versus 210 [180-260] pg/mL; p=0.011). Levels were also lower in chronic than newly diagnosed ITP. IL-33 levels are lower among active ITP (median [IQR], 105 [85 – 120] pg/mL) compared with those in complete remission (median [IQR], 240 [200 – 250] pg/mL) and healthy controls ($p<0.001$) while no significant difference was found among the two latter groups (p=0.197). Patients who had splenectomy had lower IL-33 levels than non-splenectomized ones. Lower IL-33 levels were found among patients with corticosteroid-dependence and relapse ($p<0.05$). No significant difference as regards IL-33 between treated and un-treated patients with active ITP. IL-33 was positively correlated to platelet count at sampling ($r=0.714$, $p<0.001$). **Conclusions:** Alterations of IL-33 levels in pediatric patients with ITP highlight the role of T-cell immune response in the pathogenesis of ITP. It may be considered as a potential prognostic marker for the development of chronic ITP as it correlates with disease activity. Further studies investigating the role of IL-33 in the pathogenesis of ITP may provide a new therapeutic target for ITP.