Urinary Neutrophil Gelatinase Associated Lipocalin as a Novel Biomarker of Disease Activity in Lupus Nephritis

Thesis

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BY

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List of Abbreviations

^{o} C	Degree Centigrad
^{o} F	Degree Fahrenheit
µ	Micro
APS	Antiphospholipid Antibody Syndrome
AbTPO	Antithyroid Peroxidase Antibody
ACE	Angiotensin-Converting Enzyme
ACR	American College Of Rheumatology
AHA	Autoimmune Hemolytic Anemia
AHF	Acute Heart Failure
AKI	Acute Kidney Injury
AMI	Acute Myocardial Infarction
anti-dsDNA	Anti-Double Stranded Dna Antibody
APC	Antigen Presenting Cell
ARBs	Angiotensin Receptor Blockers
AVN	Avascular Necrosis
AZA	Azathioprine
BAL	Bronchio Alveolar Lavage
BILAG	The British Isles Lupus Assessment Group Index
BLyS	B-Lymphocyte Stimulator
BSA	Body Surface Area
CBC	Complete Blood Count
CHF	Chronic Heart Failure
CLE	Cutaneous Lupus Erythematosus
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclooxygenase
CPK	Creatine Phosphokinase

CQ	Chloroquine Phosphate
CR1, 2	Complement Receptors 1, 2
CR3	Complement Receptor 3
CRP	C Reactive Protein
CS	Corticosteroids
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CVD	Cardio-Vascular Disease
CYC	Cyclophosphamide
DHEA	Dehydroepiandrosterone
DIL	Drug-Induced Lupus
DLE	Discoid Lupus Erythematosus
DNA	Deoxyribonucleic Acid
dsDNA	Double-Stranded DNA
DVT	Deep Venous Thrombosis
E2	Estradiol
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECLAM	The European Consensus Lupus Activity Measure
EEG	Electroencephelograms
ELISA	Enzyme-Linked Immunoadsorbent Assay
EM	Electron Microscopy
EMG	Electromyography
ESR	Erythrocyte Sedimentation Rate
ESRD	End-Stage Renal Disease
FA-Kinase	Focal Adhesion Kinase
FcgammaRIIA	Fcgamma Receptor Type IIA
FDA	Food And Drug Administration
G6PD	Glucose-6-Phosphate Dehydrogenase

GBM	Glomerular Basement Membranes
GERD	Gastroesophageal Reflux Disease
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HCQ	Hydroxychloroquine
HIF-1α	Hypoxia-Inducible Factor 1, Alpha Subunit
HLA	Human Leukocyte Antigen
HPA	Hypothalamic-Pituitary-Adrenal
hpf	High Power Field
Hsp90	Heat Shock Protein 90
IF	Immunofluorescence
IFN-γ	Interferon- γ
IIM	Idiopathic Inflammatory Myositis
IL	Interlukins
IP-10	Interferon-Producing Protein 10
ISN	International Society Of Nephrology
ITP	Immune Thrombocytopenic Purpura
IVC	Intravenous Cyclophosphamide
IVIG	Intravenous Immunoglobulins
kDa	Kilo Dalton
kg	Kilogram
L	Litre
LAI	The Lupus Activity Index
Lcn-2	lipocalin 2
LKM	Liver Kidney Microsome
LM	Light Microscopy
LN	Lupus Nephritis
LSP	Liver-Specific Lipoprotein
LV	Left Ventricle

MAC	Membrane Attack Complex
MBP	Mannose-Binding Protein
MCP	Metacarpophalangeal
MCP-1	Monocyte Chemoattractant Protein -1
MDCK cells	Madin Darby Canine Kidney Cells
MHC	Major Histocompatibility Complex
MMF	Mycophenolate Mofetil
MMP-9	Matrix Metalloproteinase 9
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NF-κB	Nuclear factor-kappa B
NIH	National Institutes Of Health
NMDA	N-Methyl-D-Aspartic Acid
NP-SLE	Neuropsychiatric Systemic Lupus Erythematosus
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
P/C ratio	Urine Protein to Creatinine Ratio
PBC	Primary Biliary Cirrhosis
PCNA	Proliferating Cell Nuclear Antigen
PET	Positron Emission Tomography
PIP	Proximal Interphalangeal
PLN	Proliferative Lupus Nephritis
PML	Progressive Multifocal Leukoencephalopathy
RBCs	Red Blood Cells
rIFN-γ	Recombinant Interferon-Γ
RNA	Ribonucleic Acid
RNP	Ribonucleoprotein
ROS	Reactive Oxygen Species
RPM	Round Per Minute
RPS	Renal Pathology Society

SCLE	Subacute Cutaneous Lupus Erythematosus
SLAM	Systemic Lupus Activity Measure
SLE	Systemic Lupus Erythematosus
SLEDAI	The Systemic Lupus Erythematosus Disease Activity Index
SMA	Smooth Muscle Antibody
SNPs	Single-Nucleotide Polymorphisms
SPF	Skin Protection Factor
TACI-Ig	Transmembrane Activator and Calcium-Modulator and An Immunoglobulin Chain
TGF-β	Tumor Growth Factor B
TNF	Tumor Necrosis Factor
TTP	Thrombocytopenic Purpura
uNGAL	Urinary Neutrophil Gelatinase-Associated Lipocalin
UVR	Ultraviolet Radiation
VCAM-1	Vascular Cell Adhesion Protein 1
WBCs	White Blood Cells
WHO	World Health Organization

Introduction & Aim of the Study

Systemic lupus erythematosus (SLE) is a prototype of autoimmune diseases affecting predominantly women. It is characterized by dysregulation of self-reactive B cells leading to autoantibody production against own antigens, immune complex deposition and subsequent complement activation with tissue damage ***(Rojas-Villarraga et al., 2010)*.**

SLE affects multiple organ systems including kidneys, skin, lung, heart, the hematopoietic system and brain. One of the most severe complications of SLE that is associated with significant morbidity and mortality is lupus nephritis, it may lead to persistent proteinuria, chronic renal failure and end stage renal disease ***(Bagavant and Fu, 2009)*.**

Lupus nephritis (LN) occurs in up to 50% of SLE patients. Severe LN has been reported to result in end stage kidney disease at a rate of 10-26%, which may be a result of the difficulty in recognizing a flare early enough to affect the course of the disease

since prompt diagnosis and early treatment lead to better outcomes ***(Rubinstein et al., 2010).***

Biomarkers provide the potential to non invasively evaluate and help to manage patients with lupus nephritis. Many candidates have been identified, but they require validation in larger cohorts. It is likely that combinations of biomarker profiles, rather than individual markers, will emerge to help better prediction of the severity of inflammation, the extent of fibrosis, the degree of drug responsiveness, and other variables ***(Manoharan and Madaio, 2010).***

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa iron-transporting protein in secondary granules of neutrophils. NGAL is secreted more readily from neutrophils than any other proteins and is considered as a special biomarker of neutrophil degranulation ***(Chen et al., 2009).***

NGAL is rapidly accumulating in the kidney tubules and urine after nephrotoxic and ischemic insults so it has been put forward as an early, sensitive, non-invasive biomarker for acute kidney injury (AKI) ***(Makris et al., 2009).***