The Role of Urinary Monocyte Chemoattractant Protein-١ in Monitoring Children with Lupus Nephritis

Thesis

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بِسْمِ اللَّهِ الرَّحمَنِ الرَّحيمِ

(...رَبِّ أَوزعنِي أَن أَشكُرَ نِعمَتَكَ الَّتِي
أَنْعَمْتَ عَلَيَّ و عَلى والِدَيَّ
وَأَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ وأَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

صدق الله العظيم

النمل.. اية رقم ١٩

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Feda Abd El Aziz El Farouk El Bassiouny

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List of Abbreviations

ACE : Angiotensin converting enzyme
ACR : Albumin-creatinine ratio
ACR : American College of Rheumatology
Ang : Angiotensin
anti-dsDNA: Anti-double stranded DNA
Anti-RNP : Antiribonucleoproteins
APRIL : A proliferation-inducing ligand
APS : Antiphospholipid syndrome
ARBs : Angiotensin receptor blockers
BILAG : British Isles lupus assessment group
BILD : Brief Index of Lupus Damage
BlyS/ BAFF : B-lymphocyte stimulator B-cell activating factor
CAMs : chemokine adhesion molecules
CBC : Complete blood count
CCL : C-C chemokine ligand
CCR۲ : C-C chemokine receptor
CFH : Complement factor H
CKD : Chronic kidney disease
DPLN : Diffuse proliferative LN
dsDNA : Double-stranded DNA (dsDNA)
ECLAM :European Consensus Lupus Activity Measurement
ELISA : Enzyme-linked immuno-sorbent assay
ENAS : Extractable nuclear antigen antibodies
ESR : Erythrocyte sedimentation rate
GFR : Glomerular filtration rate
HDL : High density lipoprotein
ICs : Immune complexes

List of Abbreviations *(Cont.)*

IFNc-IP-١٠ : Interferon-Inducible Protein ١٠
IL : Interleukins
ISN : International Society of Nephrology
IVIG : Intravenous immunoglobulin
LAI :Lupus Activity Index
LDL : Low density lipoprotein
LDIQ :Lupus Damage Index Questionnaire
LN : Lupus Nephritis (LN)
MBL : Mannose binding lectin
MCP-١ : Monocyte chemoattractant protine-١
MIP-١a : Macrophage inflammatory protein-١a
NGAL : Neutrophil Gelatinase-Associated Lipocalin
ET-١ : Endothelin-١
NSAIDs : Nonsteroidal anti-inflammatory drugs
PAPS : Primary antiphospholipid syndrome
PCR : Protein–creatinine ratio
RANTES : Regulated on Activation Normal T Cell Expressed
RAS : Renin angiotensin system
ROC : Receiver Operating Characteristic
RPS : Renal Pathology Society
SD : Standard deviation
SDI : Systemic lupus Damage Index (SDI).
sIL-٧R : Serum interleukin ٧ receptor
SLAM :Systemic Lupus Activity Measure
SLAQ : Systemic Lupus Erythematosus Activity Questionnaire
SLE : Systemic lupus erythematosus
SLEDAI : SLE disease Activity Index
SLICC : Systemic Lupus International Collaborating Clincs

List of Abbreviations *(Cont.)*

SPSS : Statistical Package for Social Sciences
Sβ٢ M/SCysC : Serum β٢ microglobulin/cystatin C
TCR : T-Cell Receptor
TGF-β١ : Transforming growth factor beta-١
Th : Helper
TNF : Tumor necrosis factor
TWEAK : TNF-like weak inducer of apoptosis
VEGF : Vascular endothelial growth factor
WHO : World Health Organization

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Introduction

Systemic lupus erythematosus (SLE) is a chronic auto-immune disease with multiorgan involvement. Children with SLE often have severe disease presentations including renal involvement, which ranges from asymptomatic urinary findings to acute renal failure ***(Brunner et al., ٢٠٠٨).***

Lupus Nephritis (LN) remains one of the most important factors influencing therapeutic management and long-term prognosis ***(Bogdanovic et al., ٢٠٠٤; Hobbs et al., ٢٠١٠)***. Renal involvement in patients with SLE in the form of severe LN is associated with a significant burden of morbidity and mortality. Conventional laboratory biomarkers in current use have not been very successful in anticipating disease flares, predicting renal histology, or decreasing unwanted outcomes. Since early treatment is associated with improved clinical results, it is thus essential to identify new biomarkers with substantial predictive power to reduce the serious sequel of this difficult to control lupus manifestation ***(Reyes-Thomas et al., ٢٠١١)***.

Since urine can be readily obtained, it lends itself as an obvious biological sample. Much of the focus has been on the measurement of urinary chemokines and cytokines in patients with LN. It has been reported that monocyte chemoattractant

protein-١ (MCP-١), a key chemokine involved in monocyte chemotaxis can be consistently found at high levels in the urine of patients with active LN. Moreover urinary MCP-١ levels decline with treatment of nephritis ***(Li et al., ٢٠٠٦)***. In LN, MCP-١ may play a role in modulating interstitial inflammatory process and in tubulointerstitial renal damage via transforming growth factor beta-١ (TGF-β-١) pathway ***(Wagrowska-Danilewicz et al., ٢٠٠٥)***.

Aim of the Work

The aim of this study was to evaluate the validity of the urinary monocyte chemoattractant protein-١ as a urinary biomarker in diagnosis and follow up of juvenile onset LN. Its relation to renal flare, remission and response to treatment was fully studied.

Lupus Nephritis

Lupus Nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE), which is associated with significant morbidity and mortality of SLE patients ***(Li et al., ٢٠١٣)***.

Epidemiology:

LN is present in approximately ٥٠٪-٨٠٪ of patients with pediatric SLE. In approximately ٨٥٪ of pediatric patients who have renal lupus, the nephritis is manifested within the first year after diagnosis of SLE ***(Benseler and Silverman, ٢٠٠٧).***

Children with SLE are at a higher risk of renal disease than adults and tend to sustain more disease damage secondary to more aggressive disease and treatment-associated toxicity ***(Brunner et al., ٢٠٠٨).***

AlSaleh et al. (٢٠٠٨) reported a high prevalence of LN (٥٢.٣٪) among their Arab patients, which they felt probably reflected a common characteristic in SLE patients of Middle East origin.

In a study made by ***Bakr (٢٠٠٥),*** LN was evident in ٨٠.٨٪. Also, in a study made by ***Salah et al. (٢٠٠٩),*** the prevalence of nephritis was ٦٧٪, The female to male ratio was ٢.٧ to ١ and the mean age at presentation was ١٠ +/- ٢.٧ years.