بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سامية زكى يوسف

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Serum levels of Interleukin-2 in a cohort of Egyptian systemic lupus erythematosus patients with glomerulonephritis

Thesis
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BY

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List of Abbreviations

Abb.	Full term
ACR	American College of Rheumatology
AICD	Activation-induced cell death
ANA	Antinuclear antibodies
anti-dsDNA	Anti double stranded DNA
AVN	Avascular necrosis
AZA	Azathioprine
BAFF	B cell activating factor
BCL-2	B-cell lymphoma 2
BILAG	British Isles Lupus Assessment Group Scale
Blimp1	B lymphocyte-induced maturation protein 1
BLyS	B-lymphocyte stimulator
BP	Blood pressure
BUN	Blood urea nitrogen
CAR-T	Chimeric antigen receptor
CNIs	Calcineurin inhibitors
CREB	cAMP response element-binding protein
CREM	cAMP response element modulator
CRP	Creactive protein
CVA	Cerebrovascular accidents
CYC	Cyclophosphamide
Cys	Cyclosporin
DCs	Dendritic cells
DMARDS	Disease modifying anti-rheumatic drugs
ECLAM	The European Consensus Lupus Activity Measure
ESKD	End stage kidney disease
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disease
EULAR	The European League Against Rheumatism
Fas	First apoptosis signal

FcRs.....Fc receptors
FDA.....Food and Drug Administration
FLIP.....FLICE-inhibitory protein
FSGS.....Focal segmental glomerulosclerosis
gc.....Common gamma-chain
GI.....Gastrointestinal
GWAS.....Genome-wide association studies
HB ..... Hemoglobin
HCQ.....Hydroxychloroquine
HCs.....Health controls
Ics.....Immune complexes
IF.....Immunofluorescence
IFN.....Interferon
IFNγ.....Interferon-gamma
Ikzf3.....IKAROS Family Zinc Finger 3
IL-2.....Interleukin-2
IL-2Rs..... Interleukin-2 receptors
IL-2Rα, β.....IL-2 receptor alpha, beta
ILD.....Interstitial lung disease
IPO.....Intestinal pseudo-obstruction
Iv CYC.....Intravenous cyclophosphamide
JAK .....Janus kinase
kDa.....Kilodalton
LN.....Lupus nephritis
LP.....Lupus podocytopathy
mAb.....Monoclonal antibody
MAPK.....Mitogen-activated protein kinase
MBL .....Mannose-binding lectin
MMF .....Mycophenolate mofetil
MPA.....Mycophenolic acid
NETs .....Neutrophil extracellular traps
NK.....Natural killer
NPSLE.....Neuropsychiatric lupus
P/C ratio.....Protein creatinine ratio

PH.....Pulmonary hypertension
PI3K.....Phosphoinositide 3- kinase
PLT.....Platelets.
PTEN .....Phosphatase and tensin homologue
RAAS blockers .....Renin–angiotensin–aldosterone system blockers
RCC..... Renal cell carcinoma
rhIL-2.....Recombinant human interleukin-2
RTX.....Rituximab
S.creat.....Serum creatinine.
SC.....Subcutaneous
SCLE.....Subacute cutaneous lupus erythematosus
SELENA..... The Safety of Estrogens in Lupus Erythematosus National Assessment
SLAM..... The Systemic Lupus Activity Measure
SLE.....Systemic lupus erythematosus
SLEDI-2000.....SLE disease activity index-2000
SLICC.....Systemic Lupus International Collaborating Clinics
SLS.....Shrinking lung syndrome
SOC.....Standard of care
STAT.....Signal transducer and activator of transcription
TAC.....Tacrolimus
TCGF.....T-cell growth factor
TCR .....T cell receptor
Th.....Helper T
TILs.....Tumor-infiltrating lymphocytes
TLC.....Total leucocytic count.
TLRs.....Toll-like receptors
TLSs.....Tertiary lymphoid structures
Treg.....Regulator T cells

Introduction

Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease characterized by multiple organ damage. Loss of immune tolerance is a leading characteristic of SLE. A variety of autoantibodies, immune complexes, autoreactive immune cells, and inflammatory cytokines are involved in the development of organ involvement in SLE ***(Tsokos 2011)***.

Lupus nephritis (LN) is one of the most severe manifestations of SLE that affects majority of patients and is characterized by glomerular deposition of immune complexes followed by recruitment of inflammatory cells. Immune complexes, inflammatory cells, together with elevated proinflammatory cytokines lead to irreversible kidney damage ***(Iwata et al., 2011; Davidson, 2016).***

Interleukin-2 (IL-2) is a 15 kDa α-helical cytokine predominantly produced by activated CD4+, activated CD8+ T cells, NK cells, dendritic cells, and macrophages. It is considered as an essential growth factor for T cells, especially for regulator T (Treg) cells. IL-2 is part of the body's natural response to microbial infection, and in discriminating between foreign ("non-self") and "self". IL-2 mediates its effects by binding to IL-2 receptors, which are expressed by lymphocytes (***Malek, 2008).***

The pleiotropic effects of IL-2 are enabled due to the fact that IL-2 signal can be transduced via 3 different

signaling pathways; JAK-STAT, PI3K/ Akt/ mTOR and MAPK/ ERK pathway ***(Arenas-Ramirez et al., 2015).***

Impaired IL-2 production by T cells has been confirmed in autoimmune conditions such as itchy psoriasis, lupus-prone mice models and SLE patients ***(Humrich et al., 2010; von Spee-Mayer et al., 2016; Comte et al., 2017)***. Recombinant human IL-2 (rhIL-2) has been approved by the Food and Drug Administration (FDA) and in several European countries for the treatment of cancers (melanoma, renal) in large intermittent doses and has been extensively used in continuous doses **(*Bhatia et al, 2009).***

Recent studies have improved the understanding of the role of IL-2 in restoring CD4+ Treg homeostasis and support a rationale for its use at low doses to induce Tregs and treat autoimmune diseases. Low doses of IL-2 in soluble form or coupled to anti-IL2 mAbs can also enhance Tregs, while avoiding stimulation of Teffs. A growing number of early phase clinical trials have provided Promising data about initial safety and efficacy data in various autoimmune diseases as SLE ***(He et al., 2016; von Spee-Mayer et al., 2016).***

However, the clinical relevance of intrinsic IL-2 in SLE patients is still elusive. A detailed analysis of the clinical correlation of IL-2 in SLE may help to further understand the pathogenesis of SLE and may lead to the development of novel treatment strategies.

Aim of the work

The aim of this study is to evaluate the relationship between serum Interleukin-2 (IL-2) level and renal involvement in the Systemic lupus erythematosus (SLE) patients.

Systemic Lupus Erythematous

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder of connective tissue characterized by autoantibodies that target nuclear antigens, remissions and flares, and highly variable clinical presentation, disease course, and prognosis ***(Fava and petri, 2019).***

Epidemiology:

SLE is more common in women than men across all age groups, and this female predominance is especially noteworthy in the 15-to-44-year age group, wherein the female-to-male ratio is 10 to 1 ***(Stojan and Petri, 2016).*** The disease burden of SLE is highest in Black People, followed by Asian/Pacific islanders and White People in the United States, which may be related to genetic and environmental factors. ***(Dall'Era et al., 2017)***

Little is known about the epidemiology of SLE among the Arab population worldwide or in the middle east**,** A recently published data from the Michigan Lupus Epidemiology and Surveillance Registry described a 2.1-fold higher incidence of SLE among Arab-Americans compared with non-Arab Caucasians and African Americans ***(Housey et al., 2015).***