Serum Levels of Tumor Necrosis Factor Alpha in First Degree Relatives of Systemic Lupus Erythematosus Patients

Thesis

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List of Contents

List of Abbreviations

Abbrev.	:	Meaning
ACLE	**:**	Acute cutaneous lupus erythematosus
ACR	**:**	American College of Rheumatology
ANA	**:**	Anti Nuclear Antibodies
Anti-dsDNA	**:**	Anti–double-stranded DNA
APRIL	**:**	A proliferation-inducing ligand
APSN	**:**	Antiphospholipid antibody syndrome nephropathy
BICLA	**:**	BILAG based composite Lupus Assesment
BILAG	**:**	British Isles Lupus Assessment Group Index
BLK	**:**	B lymphocyte kinase
BLyS	**:**	B-lympocyte stimulator
CCLE	**:**	Chronic cutaneous lupus eryhtematosus
CD	**:**	Cluster of differentiation
CLASI	**:**	Cutaneous lupus disease area and severity index
CVD	**:**	Cardiovascular disease
DAS28	**:**	Disease Activity Score 28
DCs	**:**	Dendritic cells
DHEAS	**:**	Dehydroepiandrosterone

ECLAM	**:**	European Consensus Lupus activity measurement
FADD	**:**	Fas-associated death domain
FDA	**:**	Food and Drug administration
FSGS	**:**	Focal segmental glomerulosclerosis
GWAS	**:**	Genome-wide association study
HLA	**:**	Human leukocyte antigens class
ICs	**:**	Immune complexes
IFN	**:**	Interferon
Ig	**:**	immunoglobulin
IL	**:**	Interleukin
IRF5	**:**	Interferon regulatory factor 5
LAI	**:**	Lupus Activity Index
LAI-P	**:**	Lupus Activity Index in Pregnancy
MHC	**:**	Major histocompatibility complex
NETs	**:**	Neutrophils
NF-kB	**:**	Nuclear factor kappa light-chain-enhancer of activated B cells
PAD	**:**	Persistent active disease
PASS	**:**	Patient acceptable symptoms state
PBMC	**:**	Peripheral blood mononuclear cells
PGA	**:**	Physician global assessment
QoL	**:**	Quality of life
RCT	**:**	Randomized controlled trials

RIP-1	**:**	Receptor-interacting serine/threonine-protein kinase 1
SACQ	**:**	Serological active clinically quiescent
SCLE	**:**	Subacute cutaneous lupus erythematosus
SELENA	**:**	Safety of estrogens in lupus erythematosus national assesment
SF	**:**	Short form
SLAM	**:**	Systemic Lupus Activity Measure
SLE	**:**	Systemic Lupus Erythematosus
SLEDAI	**:**	Systemic Lupus Erythematosus Disease Activity Index
SLE-P-DAI	**:**	SLE Pregnancy Disease Activity Index
SNPs	**:**	Single nucleotide polymorphisms
SRI	**:**	SLEDAI Responder Index
STAT4	**:**	Signal Transducer and Activator of Transcription 4
TLR	**:**	Toll-like receptor
TMA	**:**	Thrombotic microangiopathy
TNF-a	**:**	Tumor Necrosis Factor-alpha
TRADD	**:**	TNFR-associated death domain
TRAF-2	**:**	TNF receptor-associated factor-2

List of Tables

List of Figures

Introduction

Systemic lupus erythematosus (SLE) is a severe multisystem autoimmune disease which is caused by a combination of genetic and environmental factors ***(Harley et al., 2006).***

Many lines of evidence underscore the importance of cytokines in SLE susceptibility and serum tumor necrosis factor alpha is one of the most important cytokines.

Serum tumor necrosis factor alpha (TNF-α) levels are elevated in many patients with SLE ***(Weckerle et al., 2012).*** High levels of TNF-α have been correlated with increased clinical disease activity and the presence of anti-dsDNA antibodies ***(Aringer and Smolen, 2004)***. High levels of TNF-α have been demonstrated in patients with lupus nephritis, and TNF-α is overexpressed in renal tissue in lupus nephritis ***(Aringer and Smolen, 2008).*** The role of TNF-α in murine models of SLE has been controversial. In some models TNF-α improved disease features ***(Jacob and McDevitt, 1988)***, while in others TNF-α blockade has been beneficial. Small scale clinical trials in human SLE suggest that short-term TNF-α blockade may have benefit in lupus nephritis, as well as transient benefit in SLE arthritis ***(Aringer and Smolen, 2008)***.

Significant side effects have been reported in a small group of SLE patients who have received long-term anti-TNF-α therapy, and there are no large-scale trials of TNF blockade in human SLE to date ***(Aringer et al., 2009).***

It is not clear whether high TNF-α predisposes to SLE or if the levels rise after the disease is established. Genetic studies have implicated a promoter polymorphism in the TNF-α gene in SLE susceptibility ***(Pan et al., 2012),*** although the TNF-α gene is within the HLA locus which is characterized by multiple association signals that are difficult to resolve due to high linkage disequilibrium in the region. It is also not clear that the TNF-α promoter polymorphism functionally confers a propensity for excess TNF-α mRNA or protein production ***(Mekinian et al., 2012).***

In support of the idea that background genetic factors influence TNF-α levels, some non-HLA polymorphisms have been associated with differences in TNF-α in SLE patients ***(Jensen et al., 2013).***

Aim of the work

The aim of this study is to assess the serum level of tumor necrosis factor alpha in patients with systemic lupus erythematosis and first degree relatives and its relation to different clinical and laboratory disease parameters.