

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

Thesis

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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 |

List of Abbreviations

| | | |
|--------------------------------|---|--|
| 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-κB | : | 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 |

 *List of Abbreviations* 

| | |
|------------------|---|
| 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 |

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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 erythematosus and first degree relatives and its relation to different clinical and laboratory disease parameters.