ANTI-TOPOISOMERASE-I (ANTI-SCL-70) ANTIBODIES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Thesis

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بسم الله الرحمن الرحيم

"ويسئلونك عن الروح قل الروح من أمر ربي وما أوتيتم من العلم إلا قليلا"

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ABSTRACT

Systemic lupus erythematosus is a chronic, systemic, autoimmune disease of unknown etiology characterized by impaired T-cell responses and dysregulation of B-cell activation that results in the production of autoantibodies, generation of circulatory immune complexes, and activation of the complement system. **Objective:** To investigate the presence and clinical significance of anti-Scl-70 antibodies in patients with systemic lupus erythematosus (SLE) and to correlate disease activity and different clinical parameters with anti-Scl-70 antibody. **Methods:** Fifty six patients with SLE fulfilling the ACR criteria for the diagnosis of SLE and 20 healthy controls were studied. Levels of antibodies against Scl-70 were determined using enzyme-linked immunosorbent assay (ELISA). Disease activity was assessed using systemic lupus activity measure (SLAM). **Results:** The analysis performed indicated that the mean of serum anti-Scl-70 was significantly higher in the whole SLE patient group. There was significant correlation between anti-Scl-70 and renal involvement with higher frequency of renal involvement in anti-Scl-70 positive patient. The prevalence of chest involvement was significantly higher in SLE patients with anti-Scl-70. The SLAM score showed no significant correlation with anti-Scl-70. **Conclusion:** Anti-Scl-70 antibody might be present in the setting of SLE, without scleroderma features. These antibodies might be a marker of increased risk of pulmonary and renal involvement.

Keywords:

Systemic lupus erythematosus, autoantibodies, anti-Scl-70 antibodies, antitopoisomerase-I antibodies.

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LIST OF ABBREVIATIONS

Ab	Antibody
ACR	American College of Rheumatology
AECA	Anti-endothelial cell antibodies
ANA	Antinuclear antibodies
BILAG	British isles lupus assessment group
BP	Blood pressure
CBC	Complete blood count
CLIF	Crithidia luciliae indirect immunoflourescence
CNS	Central nervous system
CRP	C-reactive protein
CTD	Connective tissue disease
DNA	Deoxyribonucleic acid
Ds-DNA	Double stranded deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbent assay
ENA	Extractable nuclear antigens
ESR	Erythrocyte sedimentation rate
GBM	Glomerular basement membrane
Hct	Hematocrite
HS	Heparin sulfate
IB	Immunoblotting
ID	Immunodiffusion
Ig	Immunoglobulin
IIF	Indirect immunofluorescence
IL-6	Interleukin-6
LC SSC	Limited cutaneous systemic sclerosis
LE	Lupus erythematosus
M	Messenger
MCTD	Mixed connective tissue disease
MHC	Major histocomptability complex
MRI	Magnetic resonance imaging
NSAIDs	Non-steroidal anti-inflammatory drugs
OLS	Ordinary least squares
PAI-1	Plasminogen activator inhibitor-1
PCNA	Proliferating cell nuclear antigen
PLT	Platelet
Pol.	Polymerase
RBC	Red blood cell

RNA	Ribonucleic acid
RNA PIIO	RNA polymerase II
RNP	Ribonucleoprotein
SCLE	Subacute cutaneous lupus erythematosus
SLAM	Systemic lupus activity measure
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus activity index
Sm	Smith
SSC	Systemic sclerosis
TCR	T-cell receptors
TNF-α	Tumor necrosis factor- α
Topo-1	Topoisomerase-1
t-PA	Tissue plasminogen activator
UV	Ultraviolet
WB	Western blotting
WBC	White blood cell

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INTRODUCTION
AND
AIM OF WORK

INTRODUCTION AND AIM OF THE WORK

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease, particularly prevalent in women, with a genetic predisposition. This is triggered by contact with an environmental stimulus, resulting in the production of pathogenic autoantibodies and immune complexes which produce the pathologic features of the disease **(Kurien and Scofield, 2006)**.

The diagnosis can be definitely established if 4 of 11 American College of Rheumatology (ACR) criteria are met, serially or simultaneously **(Tan et al., 1982)**.

Antinuclear antibodies (ANAs) are a group of autoantibody specificities targeting nucleic acids and nucleoproteins found in the connective tissue disease, systemic lupus erythematosus (SLE), systemic sclerosis, mixed connective tissue disease (MCTD), and primary Sjögren's syndrome **(Peng et al., 1997)**.

ANAs against nucleolar antigens characterize the autoantibody response in systemic sclerosis. Anti-Scl-70 autoantibodies predominantly target the catalytic C-terminal region of DNA topoisomerase-I, a 100-KD helicase that relieves superhelical strain during the transcription or replication of DNA **(Peng et al., 1997)**.

Anti-Scl-70 autoantibodies are found in 20 to 35 percent of patients with systemic sclerosis (SCC), mainly in those with the diffuse form of the disease **(Russo et al., 2000)**. These

antibodies have been generally associated with a poor prognosis and have been linked to extensive skin and pulmonary fibrosis **(Steen et al., 1988)**. The presence of anti-Scl-70 antibodies is generally considered highly specific for systemic sclerosis **(Varquez-Abad et al., 1997)**. There are only a few reports in the literature describing patients who had tested positive for antitopo-I in a classic SLE **(Al-Attia and D'Souza, 2003)**.

Watanabe and co-workers reported 26 percent of patients with SLE to have antitopoisomerase-I in their serum **(Watanabe et al., 1997)** giving a speckled pattern of staining detected by enzyme linked immunosorbent assay (ELISA). In addition, case reports based on double diffusion in agar gel, and on immunoblots have also suggested that anti-Scl-70 may be present in SLE patients with **Kameda et al., 1997** or without **Stojanov et al., 1995** concomitant features of SSC. One group found anti-Scl-70 antibodies, to be present in a significant subset (25%) of patients with SLE when using ELISA **(Gussin et al., 2001)**. Moreover, serial ELISA determination of anti-Scl-70 levels correlated well with disease activity and the presence of pulmonary hypertension and nephritis **(Gussin et al., 2001)**. They concluded that anti-Scl-70 antibody is present in a significant subset (25%) of patients with SLE and it provides a very good correlate of disease activity and suggests an increased risk of pulmonary hypertension and renal involvement **(Gussin et al., 2001)**.

The presence of anti-topoisomerase-I antibodies without features of systemic sclerosis was demonstrated in SLE patients by **Hamidou and co-workers** in **2006**. The antibodies disappeared with disease remission or end stage renal disease, in correlation with dsDNA antibodies and (SLEDAI) systemic lupus erythematosus activity index. These authors found antitopoisomerase-I antibodies in 25% of SLE patients with correlation with activity index and frequency of renal involvement (68%) and pulmonary hypertension (26%). These data were confirmed in another work of the group **(Ignat et al., 2003)**. In the Birmingham lupus cohort 10.1% of SLE had anti-Scl-70 and the antibodies were significantly associated with the presence of renal damage **(Yee et al., 2003)**.

In **1993 Mukai et al.** described three patients with this antibody associated with central system involvement (CNS), but not with SSC. **Stojanov et al. (1995)**, described a patient who in addition to positive antitopoisomerase-I had antibodies to phosphoproteins RNA polymerase II (RNApIIO) and ribosomal P.

This study has been under taken in order to investigate the presence and clinical significance of anti-Scl-70 antibodies in patients with systemic lupus erythematosus and to correlate disease activity and different clinical parameters as well as anti-ds antibodies titers with anti-Scl-70 antibody.

REVIEW OF LITERATURE