Prevalence and Risk Factors for Hydroxychloroquine Retinopathy among Patients with Systemic Lupus Erythematosus

Thesis

Submitted for Partial Fulfilment of
Master Degree in ***Internal Medicine***

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2019

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr./Mohamed Salah El-din Abdel Baky****, Professor of Internal Medicine & Rheumatology, Faculty of Medicine, Ain Shams University, for his meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Prof. Dr./ Tarek Ahmed El-Mamoun****, Professor of Ophthalmology, Faculty of Medicine, Ain Shams University, for his sincere efforts, fruitful encouragement.*

I am deeply thankful to ***Dr./Rasha Mohamed Hassan****, Lecturer of Internal Medicine & Rheumatology, Faculty of Medicine, Ain Shams University, for her great help, outstanding support, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

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List of Abbreviations

Abb.	Full term
AAO	*American Academy of Ophthalmology*
ABCR	*Atp binding cassette transporter*
ABW	*Actual body weight*
ACLE	*Acute cutaneous lupus erythematosus*
ACR	*American College of Rheumatology*
AF	*Autoflourescence*
ALMS	*Aspreva Lupus Management Study*
ANA	*Antinuclear antibody*
ANCA	*Anti Neutrophil Cytoplasmic Antibody*
Anti-DNA	*Anti Deoxyribonucleic acid*
Anti-Sm	*Anti-Smith antibody*
APC	*Antigen Presenting Cell*
aPL	*Anti-phospholipid antibody*
APS	*Antiphospholipid Syndrome*
AZA	*Azathioprine*
BAFF	*B-cell activating factor*
BDCQ	*Bisdesethylchloroquine.*
BILAG	*British Isles Lupus Assessment Group*
Blys	*B-lymphocyte stimulator*
BUN	*Blood urea nitrogen*
C3	*Complement 3*
C4	*Complement 4*
CBC	*Complete blood picture*
CCLE	*Chronic cutaneous lupus eryhtematosus*
CD	*Cluster of differentiation*
CNS	*Central nervous system*
CpG	*Cytosine phosphate diester guanine*
CPK	*Creatine phospho-kinase*
CQ	*Coloroquine*
CRALBP	*Cellular retinaldyhyde binding protein*
CRBP	*Cellular retinoid binding binding protein*
CRP	*C-reactive protein*
CSA	*Cyclosporin*
CTLA-4	*Cytotoxic T-lymphocyte-associated protein 4*

List of Abbreviations cont...

Abb.	Full term
CYC	*Cyclophosphamide*
DCQ	*Desethylchloroquine*
DLE	*Discoid lupus erythematosus*
DMARD	*Disease-modifying antirheumatic drugs*
ECLAM	*European Consesus Lupus Activity Mmeasurement*
ELISA	*Enzyme-linked immunosorbent assay*
ESR	*Erythrocyte sedimentation rate*
FAF	*Fundus autoflourescence*
FAF	*Fundus autofluorescence imaging*
FDA	*Food and Drug Administration*
G6PD	*Glucose-6-phosphate dehydrogenase deficiency*
GLADEL	*Grupo Latino Americano de Estudio de Lupus Eritematoso*
HCQ	*Hydroxycholoroquine*
HEK293	*Human embryonic kidney cells*
Hgb	*Hemoglobin*
HLA	*Human leucocyte antigen*
Hpf	*High power field*
HPLC	*High-performance liquid chromatography*
HR	*Hazard Ratio*
IBW	*Ideal body weight*
IFN-γ	*Interferon gamma*
IgG	*Immunoglobulin G*
IL	*Interleukin*
IRBP	*Interphotoreceptor retinoid binding protein*
ISN	*International Society of Nephrology*
ISN/RPS	*International Society of Nephrology/ Renal Pathology Society*
LN	*Lupus nephritis*
LRAT	*Lecithin retinol acyl transferase*

List of Abbreviations cont...

Abb.	Full term
LUMINA	*Lupus in Minorities; nature versus nurture*
mfERG	*Multifocal electroretinography*
MHC	*Major histocompatibility complex*
MMF	*Mycophenolate Mofetil*
MPA	*Mycophenolic acid*
MRA	*Magnetic resonance angiography*
MRI	*Magnetic resonance imaging*
MTX	*Methotrexate*
NETs	*Neutrophil extracellular traps sequester circulating tumor cells*
NIH	*National Institute of Health*
NPSLE	*Neuropsychiatric systemic lupus erythematosus*
NSAID	*Non-steroidal anti-inflammatory drugs*
OATP1A2	*Organic anion transporting polypeptide 1A2*
OCT	*Optical coherence tomography*
OS	*Rod outer segment*
P.Ovale	*Plasmodium Ovale*
pDCs	*Plasmacytoid dendritic cells*
PIP	*Proximal inter-phalangeal*
PLT	*Platelets*
PMNs	*Polymorphonuclear cells*
RA	*Rheumatoid Arthritis*
RBC	*Red blood cell*
RCOphth	*Royal college of ophthalmogist*
RNA	*Ribonucleic acid*
RNP	*Ribonucleoprotein*
RPE	*Retinal pigmented epithlium*
SCLE	*Subacute cutaneous lupus erythematosus*
SD-OCT	*Spectral domain optical coherence tomography*

List of Abbreviations cont...

Abb.	Full term
SELENA	*Safety of Estrogens in Lupus Erythematosus - National Assessment*
SLAM	*Systemic Lupus Activity Measure*
SLE	*Systemic Lupus Erythematosus*
SLEDAI	*Systemic Lupus Eryhtematosus Disease Activity Index*
SLICC	*Systemic Lupus International Collaborating Clinics*
TB	*Tuberculosis*
TH	*T-helper*
TLR	*Toll like receptor*
TNF	*Tumor necrosis factor*
TREG	*T-regulatory cell*
UVR	*Ultraviolet rays*
VF	*Visual field*
WBC	*White blood cell*
WHO	*World health organization*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with unclear etiology that affects multiple organs and affects mostly women of childbearing age. The skin, blood vessels, kidneys, central nervous system and joints are common targets of inflammation at onset or during the course of the disease. The development of SLE is attributed to disruptions in adaptive immunity, triggered by genetic predisposing factors and environmental triggers, which lead to the loss of tolerance to self-antigens ***(Qin et al., 2016).***

SLE has a relapsing-remitting course, with patients experiencing disease activity flares over time. Aiming at flare reduction, Hydroxychloroquine is the standard treatment for most SLE patients during the entire disease course and conventional immunosuppressors are given to those with severe organ involvement ***(Inês et al., 2014).***

Hydroxychloroquine (HCQ) is an antimalarial medication that has been used for many years to reduce inflammation in the treatment of patients with multiple rheumatologic diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) ***(Stelton et al., 2013).***

Antimalarial medications (HCQ and chloroquine) are among the safest ant rheumatic medications as they are rarely associated with side effects. The most common adverse effects

are related to the gastrointestinal tract, skin, and nervous system ***(Felson et al., 1990).***

However, one of the most serious side effects is ocular toxicity, which has been found to be more common when HCQ is used for long periods of time ***(Flach, 2007).***

Therefore, there is considerable concern about the risk of ocular problems among patients treated with HCQ, and regular screening (in accordance with standard guidelines) is necessary, even in the absence of ocular symptoms. HCQ-induced ocular toxicity can occur in two distinct areas of the eye: the cornea and the macula ***(Marmor et al., 2011).***

The changes in the macula can potentially be serious, as the consequences can include loss of vision. The mechanism by which antimalarial medications cause retinal toxicity involves the binding of the drugs to the melanin in the pigmented epithelial layer of the retina, and subsequent damage to rods and cones. Retinal toxicity had been classically characterized as involving bilateral "bull's-eye" maculopathy, initial photoreceptor damage with a parafoveal distribution, and further damage with a more peripheral extramacular distribution ***(Wallace, 2010).***

The risk of developing retinal toxicity has been found to be dependent on the daily HCQ dose and the duration of use. The risk of retinal toxicity is <1% for those who use HCQ for up to 5 years and <2% for those who use HCQ for 5–10 years,