INFECTION IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS; PREVALENCE AND RISK FACTORS

Thesis

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Abstract

This work aimed to study the prevalence of infection in patients with systemic lupus erythematosus (SLE), find out the different predictors and risk factors for infection in SLE and to correlate infection with different clinical, laboratory parameters, disease activity scores and use of glucocorticoids and immunosuppressive drugs.

One hundred patients with SLE, all fulfilling the 2012 SLICC criteria for the classification of SLE. All patients included in this study were subjected to full history taking, clinical examination, laboratory investigations as well as specific investigations directed to diagnosis of infection, its site and causative organism.

Our results showed that the most common sites of infection in SLE patients were chest and skin, while the most common type of infectious organisms was bacteria. Younger age, early disease, cardiac and pulmonary involvement, high ESR, thrombocytopenia, elevated serum creatinine, elevated 24-hours urinary proteins, consumed C3 and C4, high systemic lupus erythematosus disease activity index (SLEDAI) score and use of cyclophosphamide (CYC), mycophenolate mofetil (MMF) and high dose of glucocorticoids (GC), all were associated with increased risk of infection in SLE patients. Hydroxychloroquine (HCQ) use was negatively associated with infection.

Key words:

(Systemic lupus erythematosus – infection)

Contents

List Of Abbreviations

ACR	American College of Rheumatology
AIIRD	Autoimmune inflammatory rheumatic diseases
ALT	Alanine transferase
ANA	Antinuclear antibody
Anti-ds DNA	Anti- double stranded deoxyribonucleic acid
APACHE	Acute physiology and chronic health evaluation
APCs	Antigen presenting cells
ARDS	Adult respiratory distress syndrome
ASIA	Autoimmune (auto-inflammatory) Syndrome Induced by Adjuvants
AST	Aspartate transferase
BANK	B-cell scaffold protein with ankyrin repeats gene
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
BCR	B cell antigen receptors
BLK	B lymphoid tyrosine kinase
Blys	B lymphocyte stimulator
C	Complement
C3bi	Complement 3 binding site
CAD	Coronary artery disease
CBC	Complete blood count
CD	Cluster of differentiation
CH50	50% Haemolytic Complement
CHF	Congestive heart failure
CMV	Cytomegalovirus
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CR	Complement receptors
CRP	C-reactive protein
CsA	Cyclosporine A
CSF	Cerebrospinal fluid
CT	Computed tomography
CVS	Cardiovascular system
CXR	Chest x-ray
CYC	Cyclophosphamide
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus

DMARDs	Disease modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
E. coli	Escherichia coli
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FCGR2A	Fc fragment of IgG receptor IIa
FcR	Constant fragment receptors
FUO	Fever of unknown origin
GC	Glucocorticoids
GERD	Gastroesophageal reflux disease
GIT	Gastrointestinal tract
gm	Gram
GWAS	Genome-wide association studies
HB	Hemoglobin
HBV	Hepatitis B
HCQ	Hydroxychloroquine
HCV	Hepatitis C
HDL	High density lipoproteins
HIV	Human immunodeficiency virus
HLA-DR	Human Leukocyte Antigen - antigen D Related
HPV	Human papilloma virus
HSV	Herpes simplex virus
HZV	Herpes zoster virus
IA	Invasive aspergillosis
IC	Immune complex
ICAM	Intercellular adhesion molecule
ICOS	Inducible costimulator
ICU	Intensive care unit
IFN	Interferon
IgM	Immunoglobulin M
IGRA	Interferon gamma release assay
IL	Interleukin
IRAK	Interleukin receptor-associated kinase
IRF	Interferon regulatory factor
ITAM	Immuno-tyrosine activation motif
ITGAM	Integrin alpha M
IV	Intravenous

IVIG	Intravenous immunoglobulins
kg	Kilogram
KLK	Kallikrein
MBL	Mannose-binding lectin
mDCs	myeloid dendritic cells
MMF	Mycophenolate mofetil
MR	Magnetic resonant
NETs	Neutrophil extracellular traps
NF-kB	Nuclear factor kappa B
NHL	Non-Hodgkin lymphoma
NIH	National Institutes of Health
NK	Natural killer
NPSLE	Neuropsychiatric systemic lupus erythematosus
NSAIDs	Non-steroidal anti-inflammatory drugs
NTM	Non-tuberculous Mycobacterium
OPSI	Overwhelming post-splenectomy infection
OX40L	OX40 ligand
P2	Pulmonary area 2
PCR	Polymerase chain reaction
PCT	Procalcitonin
pDCs	plasmacytoid dendritic cells
PGE	Prostaglandin-E
PJP	Pneumocystis jiroveci pneumonia
PLTs	Platelets
PMNs	Polymorphonuclear leukocytes
23-PPV	23-valent polysaccharide pneumococcal vaccination
PTPN	Protein tyrosine phosphatase
PXK	PX Domain Containing Serine/Threonine Kinase
RNA	Ribonucleic acid
S.D.	Standard deviation
SCLE	Subacute cutaneous lupus erythematosus
SJS	Stevens Johnson Syndrome
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SNP	Single nucleotide polymorphism
SPP	Secreted phosphoprotein 1
SPSS	Statistical Package for the Social Science
STAT	Signal transducer and activator of transcription

TB	Tuberculosis
TEN	Toxic Epidermal Necrolysis
TLC	Total leucocytic count
TLR	Toll-like receptors
TMP-SMX	Trimethoprim-sulfamethoxazole
TNFAIP	Tumour necrosis factor-**α**-induced protein
TNF-**α**	Tumor necrosis factor-**α**
UTI	Urinary tract infection
VPI	Vaccine-preventable infections
VZV	Varicella zoster virus
WBC	White blood cells
χ^2	Chi-Square

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INTRODUCTION

SLE is a heterogeneous autoimmune disease that may involve many different organs and display a variable clinical course **(Kuo et al., 2015)**.

The pathogenesis of SLE is complex and still largely unknown. Genetic, environmental, and hormonal factors contribute to disease susceptibility **(Marques et al., 2016)**.

The diagnosis of SLE is based on characteristic clinical findings of the skin, joints, kidneys, and the central nervous system, as well as on serological parameters such as antinuclear antibodies (ANA) **(Petri et al., 2012)**.

In milder, non-organ threatening disease, antimalarials, low dose steroids, and transient use of NSAIDs is usually effective. For organ threatening disease or illness that is not responding to low doses of GC, immunosuppressants are added **(Kuhn et al., 2015)**. MMF or CYC are usually used as the first line treatment for most of severe cases, in addition to GC. For maintenance therapy, either mycophenolate mofetil or azathioprine is preferred **(Aringer et al., 2013)**. For refractory disease, biologics and antibody inhibiting strategies, such as IVIG or plasma exchange can be used **(Ding and Gordon, 2013)**.

Infections are common in SLE patients and have a great impact on morbidity and mortality. They represent about a quarter of overall mortality in this disease, and up to half of all patients experience at least one severe infection during their course of the disease **(Mok et al., 2011)**.

Types of infections in SLE patients vary widely. They may be bacterial, viral, fungal or even parasitic. Studies, done in this field, have shown that bacterial infections are the most common. Of bacterial infections, streptococcus pneumoniae infection has the highest incidence. It should be known that respiratory tract is the commonest site of infection **(Lee et al., 2013)**.

Infection affects SLE course deeply and most of hospital and ICU admissions of SLE patients are caused by infection. Complications of infection in SLE are more frequent and severe than matched controls in different studies. This can be, mainly, explained by their immunocompromised state **(Fei et al., 2014)**.

Some, and not all, of these complications are increasing susceptibility to infection by other organisms at the same time, bactraemia, septicaemia, fibrosis with loss of organ function, and sometimes disseminated intravascular coagulopathy (DIC) **(Feldman et al., 2015)**. Not only the infection, itself, that causes morbidity in SLE, but also treatment of infection can cause some complications **(Barrera-Vargas et al., 2014)**.

Therefore it is important to identify risk factors for infection in the management of SLE patients. Risk factors modification or prophylactic antibiotics use could decrease the incidence or severity of infection, improving the prognosis for SLE patients **(Danza and Ruiz-Irastorza, 2013)**.

Genetic risk factors include complement abnormalities, mannose-binding lectin (MBL) defects, C-reactive protein (CRP) deficiency,

immunoglobulin abnormalities and defects in cellular immunity **(Prabu and Agrawal, 2010)**.

Risk factors for incidence of infection in SLE may be acquired. Acquired risk factors are GC and immunosuppressive therapy, renal and vascular involvement **(Arnaud et al., 2011)**.

SLE activity has a clinical picture mimicking, to a large extent, that of infection and in most of times, they cannot be differentiated from each other. Differentiation between the two conditions, either clinical or laboratory, is very important and should be done as early as possible because early correct intervention largely affects the outcome of management regarding both disease flare and infection **(Rigante et al., 2014)**.

Finally, we should follow preventive measures to lessen the burden of infection and its complications in SLE. For prevention and decreasing frequency of infectious episodes in SLE patients, general measures as good hygiene and avoiding sources of infection, should be taken into consideration. Judicious use of GC and immunosuppressants is among methods for prevention of infection. Vaccination and chemoprophylaxis should be used when indicated **(Pasoto et al., 2014).**

AIM OF THE WORK

- To study the prevalence of infection in SLE patients.
- To find out different risk factors of infection in SLE patients.