بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

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MONA MAGHRABY

Effect of Colchicine on Serum Levels of the Inflammatory Markers: C-Reactive Protein and Interleukin-6 in Patients with Chronic Rheumatic Heart Disease

Thesis

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Mahmoud Saied

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
ARF	Acute rheumatic fever
CD4	Helper T lymphocytes
CD8	Cytotoxic T cells
CNS	Central nerve system
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythtocyte sedimentation rate
GA	Gestational age
GAS	Group A beta-haemolytic streptococci
IKBs	Inhibitory protiens
IL	Interleukin
LAVi	Left atrial volume index
MASP	MBL-associated serine proteases
MBL	Mannose-binding lectin
MHC	Major histocompatibility complex
NF-KB	Nuclear factor kappa B
NYHA	New York Heart Association
RHD	Rheumatic heart disease
SEC	Spontaneous echo contrast
TGF-β	Transforming growth factor-β
TNF	Tumor necrosis factor
Treg	T regulatory
VNTRs	Variable number of tandem repeats

INTRODUCTION

Rheumatic fever is a systemic autoimmune disorder related to prior streptococcal infection and is the leading cause of acquired heart disease in those under the age of 40 years living in developing nations. The incidence of rheumatic fever and prevalence of rheumatic heart disease vary substantially among countries. It is an inflammatory reaction that occurs approximately 10 to 21 days after throat infection with virulent strains of Group A beta-haemolytic streptococci. It affects large joints (arthritis), the heart (carditis) and less frequently the brain (chorea), skin (erythema marginatum) and subcutaneous tissues. Rheumatic heart disease refers to the functional and structural changes of the heart muscle and valves affected by rheumatic fever. [(1)]

Rheumatic fever has a marked tendency to recur following new group A streptococcal upper respiratory tract infection. Recurrence has a high risk of chronic heart lesions or worsening lesions in patients with previous rheumatic heart disease. The severity of rheumatic heart disease and the prognosis depend on the extent of the carditis and the frequency of recurrent attacks. There is much evidence from randomized controlled trials concerning the primary prevention of rheumatic fever or the treatment of pharyngitis caused by Group A beta-haemolytic streptococci (GAS) but less data is available concerning secondary prevention of the disease. [(1)]

C-reactive protein (CRP) is increased in patients with acute rheumatic fever; High levels of hs-CRP in patients with chronic rheumatic valve disease indicate the persistence of inflammation in the chronic phase. [(2)]

Inflammatory cytokines, as TNFa, IL-8 and IL-6, may play a pathogenic role in rheumatic fever. [(3)]

Inflammation is an important contributor to the pathogenesis of rheumatic heart disease, RHD a disorder of heart valves caused by a combination of immune, genetic and environmental factors. Cytokines are important mediators of inflammatory and immune responses. The role of cytokine gene polymorphisms and their potential usefulness as biomarkers in RHD patients as TNF-α and IL-6 gene polymorphisms may be useful markers for the identification of individuals susceptible to RHD, these individuals could be provided aggressive prophylactic intervention to prevent the morbidity and mortality associated with RHD. [(4)]

Aim of the Study

To assess the effect of colchicine as an anti-inflammatory drug on serum levels of inflammatory markers CRP and IL-6 in patient with chronic rheumatic heart disease. Thus possible ameliorating of the chronic inflammatory state in chronic RHD.

Colchicine is an anti-inflammatory agent which is widely used for the treatment of gout and also used extensively for familial Mediterranean fever, Behcet's disease and pericarditis. Its use in the management of gout has increased due to the widespread recommendation that it be used as a gout flare prophylaxis when urate-lowering therapy is initiated. It is used continuously for long periods of time in individuals with familial Mediterranean fever and Behcet's disease. **(61)**

Recently, The COLCOT clinical trial studied the efficacy and safety of colchicine after a myocardial infarction the authors concluded that colchicine may be effective following a myocardial infarction to decrease the risk of recurrent ischemic events. In addition, the colchicine appears to be well tolerated and safe in the short term. **(61)**

Chapter 1

SERUM INFLAMMATORY MARKERS

Role of CRP as inflammatory mediator:

C-reactive protein (CRP) secreted by the liver in response to inflammation, tissue injury and infection. It decreases rapidly after resolution of the condition. It plays a role in the innate immune system by binding to Fc receptors and acting as opsonin for pathogens which lead to release of proinflammatory cytokines. [(5)]

C-reactive protein (CRP) is an acute phase protein which rises in response to inflammation. CRP binds to phosphocholine in damaged tissues, nuclear antigens and to certain types of organisms.

C-reactive protein (CRP) binds to stimulatory receptors (Fc gammaRI and FcgammaRIIa) increasing phagocytosis and cytokines release, and binds to inhibitory receptor (FcgammaRIIb) which blocks the activatory signal. [(6)]

C-reactive protein (CRP) rises 4-6 hours after inflammatory trigger and reaches its peak after 36-50 hours. [(7)]

With the resolution of inflammatory trigger CRP levels decrease with relatively short half-life of 18 hours, this half-life is constant so it determines severity of the underlying cause. CRP rises with many conditions such as inflammation,

infection, trauma, tissue damage, malignancies and autoimmune diseases so elevation of CRP is not diagnostic for specific disease but it is beneficial as a screening test. [8]

Role of interleukins as inflammatory mediators:

Interleukins are cytokines that have an important role in immune response; they are released by helper T lymphocytes (CD4+), monocytes, macrophages and endothelial cells.

Interleukins help in development and differentiation of T and B lymphocytes and hematopoietic cells. [9]

Immunocytes exchange signals among themselves. Some signals are due to direct contact between cells. Others are through chemical messengers called cytokines which circulate in blood. [10]

Interleukin-6:

IL-6 is released as a result of tissue damage or inflammation through stimulation of acute phase reactions and hematopoiesis and its release is stopped when homeostasis is restored. IL-6 is considered inducer of acute phase reactants and show correlation with CRP. [3] Desregulated continuous release of IL-6 occur in autoimmune diseases, chronic inflammatory diseases and cancers. [11]

IL-6 is one of most important inflammatory cytokines, it has a unique signalling through two pathways, one is via a