A Study of Serum Survivin in Patients with Systemic Onset Juvenile Idiopathic Arthritis

Thesis

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بسم الله الرحمن الرحيم
﴿رَبَّنَا إِنَّنَا سَمِعْنَا مُنَادِيًا يُنَادِي
لِلْإِيمَانِ أَنْ آمِنُوا بِرَبِّكُمْ فَآمَنَّا
رَبَّنَا فَاغْفِرْ لَنَا ذُنُوبَنَا وَكَفِّرْ عَنَّا
سَيِّئَاتِنَا وَتَوَفَّنَا مَعَ الْأَبْرَارِ﴾
[سورة آل عمران: ١٩٣]

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List of Abbreviations

ACR.....American College of Rheumatology.

BIR .....Baculovirus IAP repeat domain.

BIRC .....Baculoviral IAP repeat-containing protein 2

BM.....Bone marrow.

CD .....Cluster of differentiation.

CMV.....Cytomegalo virus.

CNS .....Central nervous system.

COX ..... Cyclooxygenase.

CRP .....C reactive protein.

CTLA4 .....Cytotoxic T- cell associated protein 4

CTLs.....Cytotoxic T lymphocytes.

CyA .....Cyclosporin A.

DM .....Diabetes milletus.

DMARDS.....Disease modifying anti rheumatoid drugs.

ELISA.....Enzyme linked immunosorbent assay.

ERA.....Early rheumatoid arthritis.

ESR .....Erythrocyte sedimentation rate.

EULAR.....European League Against Rheumatism.

HLH.....Hemophagocyticlymphohistiocytosis.

IAP .....Inhibitors of apoptosis family of proteins.

IFN .....Interferon.

IL .....Interleukin.

ILAR.....International League of Associations for Rheumatology.

JIA .....Juvenile idiopathic arthritis.

LCMV .....lymphocyte choriomeningitis virus.

MMP-3 .....Matrix metalloproteinase-3.

MTX.....Methotrexate.

List of Abbreviations (Cont ..)

NK .....Natural killer cells.

NSAIDS .....Non steroidal anti inflammatory drugs.

P53.....Tumor suppressor protein 53.

PBMCs .....Peripheral blood monocytes.

PRINTO..... The Pediatrics Rheumatology International Trials Organization.

PT .....Prothrombin time.

PTT.....Partial thromboplastin time.

RA .....Rheumatoid arthritis.

RF .....Rheumatoid factor.

S100A12.....Calcium binding protein S100.

sCD.....Soluble cluster of differentiation.

SDAI.....Simplified disease activity index.

sIL-2Ra..... Soluble interleukin-2 receptor a.

siRNA.....Small interfering RNA.

SJIA.....Systemic Juvenile idiopathic arthritis.

SMAC..... SMAC; second mitochondria derived activator of caspases.

Th1 .....T helper lymphocyte 1.

TMJ .....Temporo mandibular joint.

TNF .....Tumor necrosis factor.

TNFR..... Tumor necrosis factor receptor.

TRAIL .....Tumor necrosis factor related apoptosis inducing ligand.

VEGF .....Vascular endothelial growth factor.

WT SURVIVIN.....Survivin Wild type.

XIAP.....X-linked inhibitors of apoptosis family of proteins.

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatic disease in childhood, affecting one in 1000 children ***(Duurland and Wedderburn, 2014)***. JIA is characterized by severe joint inflammation in one or more joints, which persists for at least six weeks, with disease onset before the age of 16 years. This heterogeneous group of diseases can be divided into several subtypes on the basis of clinical symptoms, medical history, and abnormalities in laboratory measures ***(Ravelli and Martini, 2007)***.

Approximately 10% of children with systemic JIA develop overt clinical features of macrophage activation syndrome (MAS), a life-threatening condition characterized by fever, organomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and coagulopathy, among other findings ***(Martini, 2012)***. The mortality rate for children hospitalized with systemic JIA and MAS is estimated to be as high as 6%, but may even be higher based on estimates from case series ***(Bennetti et al., 2012)***.

NK cells and cytotoxic T lymphocytes (CTLs) cells may be directly involved in induction of apoptosis of activated macrophages and T cells during the contraction

stage of the immune response ***(Kagi et al., 1999)***. Cytotoxic cell dysfunction leads to persistent expansion of T cells and macrophages and escalating production of proinflammatory cytokines explaining largely the clinical findings during the acute phase of MAS ***(Grom and Mellins, 2010)***.

Rheumatoid arthritis (RA) is characterized at the synovial lining hyperplasia, angiogensis, and mononuclear cell infiltrates in which there may be an imbalance between growth and death of fibFibroblastssonlast-like synoviocytes ***(Fan et al., 2010)***. A failure of apoptotic pathways may explain these pathological changes in RA synovial tissues ***(Smith et al., 2010)***.

Survivin is known as an inhibitor of apoptosis and a positive regulator of cell division ***(Andersson et al., 2012)***. It also plays an important role in the hyperplastic growth of tissues and tumors ***(Ahn et al., 2010)***.

The uncontrolled spread of destructive joint inflammation in RA resembling malignancy together with the strong correlation between inflammation and predisposition for cancer ***(Svensson et al., 2010)*** gives survivin (a proto-oncogene) a predictor value for joint destruction in patients with rheumatoid arthritis ***(Andersson et al., 2012)***.

High survivin levels are associated with severe radiographic damage at the start of treatment and a poor response to infliximab and based on this survivin measurement might be considered an additional tool for aiding the selection and follow-up of antirheumatic treatment ***(Isgren et al., 2012)***

Aim of the Study

This study aims to evaluate serum level of survivin as an anti-apoptosis marker in relation to disease activity, degree of joint destruction, and evolution of macrophage activation syndrome (MAS) in patients with systemic onset juvenile idiopathic arthritis (SJIA). The ultimate objective is to assess the prognostic gain from adding this marker to the work up of this disease.

Systemic Juvenile Idiopathic Arthritis

Definition and Epidemiology:

Systemic juvenile idiopathic arthritis (sJIA, formerly called Still's disease or systemic juvenile rheumatoid arthritis) is officially classified as a heterogeneous form of arthritis in childhood. SJIA is a subset of JIA that includes patients with characteristic daily (quotidien) fever spiking to more than 39°C (102.2°F) for 2 weeks or greater in association with arthritis of 1 or more joints ***(Petty et al., 2001)***.

SJIA accounts for approximately 10 to 20 % of all cases of JIA. It typically affects both sexes equally and may present in children as young as one year of age or younger. Patients with sJIA fall into the category of systemic arthritis in the 2004 when the International League of Associations for Rheumatology (ILAR) proposed classification of the childhood arthritides ***(Nigrovic, 2014).***

JIA is the most common chronic rheumatic disease in childhood with an incidence of 1 in 1000. Up to 1/3 of children are reported to have active disease progressing into adulthood. Although systemic JIA (sJIA) accounts only 10-20 % of all types of JIA, it has the highest morbidity

compared with other JIA subtypes and contributes about two thirds of the total mortality rate in JIA ***(Gurion, 2012)***.

In Egypt, it has been found that the prevalence of JIA amongst 10–15 year old school children was equivalent to 3.3 per 1000. Many clinicians fail to recognize JIA and therefore these children do not make their way to medical care in large study centers, therefore underestimating the true prevalence ***(Omar et al., 2013)***.

Secondary complications (e.g. growth failure, osteoporosis, deformities, and loss of function) and amyloidosis are the medical sequelae, but there are also serious developmental and social consequences. The medical treatment of patients who are at the more severe end of the disease spectrum is unsatisfactory; however, new therapies that might improve prognosis, such as autologous stem-cell transplantation and approaches for blocking interleukin-6 signaling are now widespread ***(Robinson, 2016)***.

This illness is a unique condition closer to the autoinflammatory family of diseases, with distinct manifestations and treatment responses that distinguish it from the other diseases categorized as JIA ***(Prakken, 2011).***