Serum and Synovial Fluid Level of Interleukin-17 in Correlation with Disease Activity in Patients with Rheumatoid Arthritis

Thesis Submitted for partial fulfillment for the Master degree in Rheumatology and Rehabilitation

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Abstract

Rheumatoid arthritis is a chronic inflammatory autoimmune disease of unknown etiology, many cytokines play an important role in the pathogenesis of RA, and they include TNF-α, IL-1, IL-6 and IL-17 which is a novel pro-inflammatory cytokine that plays an important role in initiation and progression of cartilage and bone destruction.

Objective: The aim of the present study was to measure serum and synovial levels of IL-17 in patients with RA; assessment of disease activity and severity using modified Ritchie articular index, DAS-28 scoring system and Functional status assessment; and correlation of serum and synovial levels of IL-17 with RA disease activity parameters.

Methods: The present study comprised two groups: Group I consists of thirty adult active RA patients with knee effusion and receiving DMARDs therapy (22 females and 8 males), with age ranged from 22 to 64 years with a mean of 41.47±11.49 years and disease duration ranging from 3 to 20 years with a mean of 9.5±4.16 years. Group II consists of thirteen healthy adults (10 females and 3 males) with age ranging from 20 to 60 years with a mean of 39.08 ± 14.19 years, served as a control group.

Results: RA patients showed a statistically significant higher mean serum IL-17 level than healthy controls (11.25 ± 9.67 versus 0.6 ± 1.4 pg/ml, respectively, p=0). In addition, synovial IL-17 levels showed a statistically significant positive correlation with serum IL-17 levels (r=0.5 and p=0.005). No significant correlations were found between both serum and synovial IL-17 levels and patients' ages, age at disease onset and disease duration. RA patients with negative RF had non-significantly higher mean serum IL-17 levels (12 ± 9.86 pg/ml) compared to those with positive RF (10.82 ± 9.81 pg/ml and p = 0.839), however, the mean synovial IL-17 levels were nearly the same. Statistically significant positive correlations were found between both serum and synovial IL-17 levels and DAS-28 scores (r = 0.556, 0.392 and p = 0.001, 0.032, respectively). RA patients with classes III and IV functional status showed statistically significantly higher mean serum IL-17 levels (17.53 ± 13.43 pg/ml) than classes I and II (8.97 ± 6.97 pg/ml and p = 0.009).

Conclusion: We can conclude that serum and synovial IL-17 levels are elevated in patients with RA which parallels the degree of disease activity and can be used as a specific marker for more aggressive joint involvement &damage.

Key words: *Rheumatoid arthritis, cytokines, serum & synovial interleukin-17, DAS-28 scoring & functional status assessment.*

Contents

List of Abbreviations

aa	Amino acid
ACR	American College of Rheumatology
AI	Articular index
ALT	Serum alanine transaminase
ANA	Antinuclear antibodies
Anti-ccp	Anti-cyclic citrullinated peptide
APCs	Antigen presenting cells
ARA	The American Rheumatism Association
AST	Serum aspirate transaminase
A-V block	Atrioventricular block
C3	Complement 3
CBC	Complete blood cell count
Chond/OC	Chondrocytes and osteoclasts
CMC	Carpometacarpal
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPT	Corticosteroid Pulse therapy
CRP	C -reactive protein
CTLA8	Cytotoxic T Lymphocyte Antigen 8
DAS-28	Disease activity score including 28-joint count
DCs	Dendritic cells
dcSSc	Diffuse cutaneous systemic sclerosis
DIP	Distal interphalangeal
DMARDs	Disease-modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
EBNA	Epstein Barr virus nuclear antigen
ELISA	Enzyme Linked Immunosorbent Assay
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate
FGF	Fibroblast growth factor
FLSs	Fibroblast- like synoviocytes

GAG	Glycosaminoglycan
GC	Glucocorticoid
GCP-2	Granulocyte chemotactic protein-2
G-CSF	Granulocyte colony-stimulating factor
GH	General health
GIT	Gastrointestinal tract
GM-CSF	Granulocyte- monocyte colony- stimulating factor
GRO- α	Growth related oncogene-α
Hb	Hemoglobin
HBV	Hepatitis B virus
hnRNP	Heterogeneous nuclear ribonucleoprotein
ICAM-1	Intracellular adhesion molecule-1
IFN	Interferon
Ig	Immunoglobulin
IkB	Inhibitory kappa B
IL	Interleukin
ILD	Interstitial lung disease
IM	Intramuscular
IPF	Interstitial pulmonary fibrosis
IV	Intravenous
JNK	c-Jun N-terminal kinase
kDa	Kilodalton
lcSSc	Limited cutaneous systemic sclerosis
MAPKs	Mitogen-activated protein kinases
MCP	Metacarpophalangeal
MCP-1	Monocyte chemoattractant protein-1
MHC	Major histocompatability complex
MIP-3α	Macrophage inflammatory protein-3 α
MMPs	Matrix metalloproteinases
Mono/Mac	Monocytes and macrophages
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTP	Metatarsophalangeal
MTX	Methotrexate

NF-kB	Nuclear factor kappa B
NK	Natural killer
NO	Nitric oxide
NS	Non significant
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
ODF	Osteoclast differentiation factor
OPG	Osteoprotegerin
PB	Peripheral blood
PBMCs	Peripheral blood mononuclear cells
PGE2	Prostaglandin E2
PIP	Proximal interphalangeal
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor-kappa B ligand
RANTES	Regulated on activation, normal T expressed and secreted
RF	Rheumatoid factor
ROM	Range of motion
RV	Right ventricle
SA	Spondyloarthropathy
SC	Subcutaneous
SCF	Stem cell factor
SD	Standerd deviation
SF	Synovial fluid
SJC	Swollen joint count
SLE	Systemic lupus erethematosus
SLEDAI	SLE Disease Activity Index
SSc	Systemic sclerosis
sTNFR	Soluble TNF receptor
TB	Tuberculosis
TGF	Tumour growth factor
TH	T helper cells
TJC	Tender joint count
TLC	Total leucocytic count

TLR4	Toll-like receptor 4
TNF	Tumour necrosis factor
TRAF6	Tumour necrosis factor receptor-associated factor-6
UL	Upper limb
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WBCs	White blood cells

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Introduction & Aim of the work

Introduction & Aim of work

Rheumatoid Arthritis is a chronic systemic autoimmune inflammatory disease characterized by synovitis, serositis, rheumatoid nodules and vasculitis. The hallmark feature of the disease is persistent symmetric polyarthritis that affect the hands and feet resulting in pain, stiffness and swelling of joints. RA causes joint destruction and thus often leads to considerable morbidity and mortality. The primary targets of inflammation are synovial membranes and articular structures. Other organs such as the skin, heart, lungs, and eyes are affected as well ***(Lee, et al., 2007)***.

Cytokines play an important role in the pathogenesis of RA, they regulate a broad range of inflammatory processes that are implicated in the pathogenesis of RA. In rheumatoid joints, it is well known that an imbalance between pro- and anti-inflammatory activities favors the induction of autoimmunity, chronic inflammation and joint damage ***(Mcinnes and Schett, 2007)***.

Many cytokines are activated in the synovium by various cell populations, they include TNF-α and IL-1 which constitute the therapeutic targets of several compounds for RA. Another proinflammatory cytokine, IL-6, which can be induced by both TNF-α and IL-1 has been implicated in pathogenesis of RA ***(Lars et al., 2009)***.

IL-17 is a novel pro-inflammatory T cell cytokine expressed in the synovium and synovial fluid of patients with RA. It is produced by activated memory CD4+T cells. IL-17 is a potent inducer of various cytokines such TNF-α and IL-1, it shares properties with IL-1 and TNF-α, it may induce joint inflammation and bone and cartilage destruction. It increases IL-6 production, induces collagen degradation and decreases collagen synthesis by synovium

and cartilage and proteoglycan synthesis in cartilage. IL-17 is also able to increase bone destruction and reduce its formation ***(Kramer and Gaffen, 2007)***.

IL-23 promotes the production of IL-17 and a strong correlation between IL-15 and IL-17 levels in synovial fluid has been observed. IL-17 has the capacity to induce joint destruction in an IL-1-independent manner and can bypass TNF-dependent arthritis ***(Lubberts et al., 2005)***.

Neutralization of inflammatory mediators to reduce progression of RA has been used successfully for several cytokines, particularly TNF-α. IL-17 is also an important mediator of RA pathology, as blockade of IL-17 in arthritis models reduces joint inflammation and bone erosion. So, Anti-IL-17 cytokine therapy is of interest as an additional new anti-rheumatic strategy for RA ***(Sarah, 2004)***.

Aim of work:

Assessment of the value of IL-17 as a specific marker of joint involvement & damage in patients with RA through the;

- Measurement of serum and synovial levels of IL-17 in patients with RA.
- Assessment of disease activity and severity using modified Ritchie articular index, DAS-28 scoring system and Functional status assessment.
- Correlation of serum and synovial levels of IL-17 with various laboratory and clinical RA disease parameters.