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

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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

	Page
Introduction and Aim of the work	1
Review of Literature	3
I- Rheumatoid arthritis	3
II- Cytokines and Rheumatoid Arthritis	35
III- IL-17 and Rheumatoid Arthritis	53
IV- IL-17 and Other Autoimmune Diseases	69
Materials and Methods	74
Results	90
Discussion	100
Summary and Conclusion	119
References	126
Arabic Summary	

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 ImmunoglobulinIkB 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 sclerosisMAPKs Mitogen-activated protein kinases

MCP Metacarpophalangeal

MCP-1 Monocyte chemoattractant protein-1
MHC Major histocompatability complex
MIP 3a Magraphaga inflammatory protein 3

MIP-3 α Macrophage inflammatory protein-3 α

MMPs Matrix metalloproteinases

Mono/Mac Monocytes and macrophagesMRI Magnetic resonance imagingmRNA Messenger ribonucleic acid

MTP Metatarsophalangeal

MTX Methotrexate

NF-kB Nuclear factor kappa B

NK Natural killerNO Nitric oxide

NS Non significant

NSAIDs Nonsteroidal anti-inflammatory drugs

OA Osteoarthritis

ODF Osteoclast differentiation factor

OPG OsteoprotegerinPB 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 factorROM Range of motionRV Right ventricle

SA Spondyloarthropathy

SC SubcutaneousSCF Stem cell factorSD Standerd deviationSF 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

List of Tables

Tabl	Table Page	
1)	List of cytokines35	
2)	The IL-17 superfamily: cellular sources, receptors, and major functions.54	
3)	Overview of the Human IL-17 Family of Cytokines54	
4)	Overview of the Human IL-17 Receptor Family56	
5)	Effect of molecules induced by IL-17 from human cells62	
6)	ARA 1987 revised criteria for the classification of rheumatoid arthritis74	
7)	Demographic features of the study group (n=30)90	
8)	Baseline clinical manifestations of the RA patients91	
9)	Main laboratory parameters of RA patients93	
10)	Assessment of disease activity of RA patients using various parameters.95	
11)	Administered Medications by the study RA population96	
12)	Serum IL-17 levels in RA patients and controls98	
13)	Correlation between serum and synovial IL-17 levels and demographic features of the RA patients	
14)	Correlation between serum and synovial IL-17 levels and RA patients' laboratory parameters	

15)	Comparison between mean serum and synovial IL-17 levels in RF +ve
	and –ve patients' groups102
16)	Comparison between mean serum and synovial IL-17 levels and duration of morning stiffness
17)	Correlations between serum and synovial IL-17 levels and parameters of RA disease activity
18)	Comparison between the mean serum and synovial IL-17 levels in RA patients' groups regarding the values of DAS-28 score
19)	Comparison between the mean serum and synovial IL-17 levels in RA patients' groups regarding the classification of functional status109

List of Figures

Fig	Page
1)	Schematic overview of the role of IL-17/Th17 in relation with other key
	cytokines and the cellular pathways of synovitis and concomitant join
	destruction
2)	Schematic overview of the mechanism of IL-17 in bone resorption. The
	interrelationship of IL-17 with RANKL, IL-1, TNF and the modulatory
	role of IL-4 and OPG is presented67
3)	Pro-inflammatory effects of interleukin-17
4)	Potential impact of Th17 cells on systemic lupus erythematosus71
5)	Plain X-ray hands (A-P) view of RA patient showing bilateral joint
	space narrowing of CMCs, MCPs and PIPs, juxta-articular osteopenia and
	ulnar deviation and sublaxation of of MCPs92
6)	RA patients' groups according to DAS-28 scoring system94
7)	Classification of the functional status of RA patients95
8)	Plain X-ray hands (A-P) views of two RA patients showing juxta-articular
	osteopenia and joint spaces narrowing97
9)	Mean serum IL-17 levels in RA patients and controls
10)	Correlation between serum and synovial IL-17 levels in RA patients 99
11)	A graph representing the comparison between the mean serum and
	synovial IL-17 levels in the two RA groups according to duration of
	morning stiffness
12)	Correlation between serum IL-17 levels and DAS-28 scores
13)	Correlation between synovial IL-17 levels and DAS-28 scores
14)	Correlation between serum IL-17 levels and TJC
15)	Correlation between synovial IL-17 levels and TJC

16)	A graph representing the comparison between the mean serum and
	synovial IL-17 levels in RA patients' groups regarding the values of
	DAS-28 score
17)	A graph showing the comparison between the mean serum and synovial
	IL-17 levels in RA patients' groups regarding the classification of
	functional status

Introduction & Film 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.