IL-17A – A PROMISING BIOMARKER FOR DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS PATIENTS

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ABSTRACT

Recent studies revealed the role of Th17 cells and IL-17A in the pathogenesis of rheumatoid arthritis (RA). However, the clinical usefulness of IL-17 at different stages in the development and progression of RA needs further investigation, including its implication in the diagnostic process or of the patients follow up.

Aims: Our study aimed to assess the systemic and local concentrations of IL-17 in RA, compared to osteoarthritis (OA) patients and healthy controls (HCs) and to establish a possible systemic and local biomarker for RA disease activity and severity.

Methods: A total of fifty-one persons were recruited to the study. Concentrations of IL-17A were assessed in matched serum and synovial fluid(SF) samples from twenty RA patients; and serum samples of fifteen OA patients and sixteen HCs. RA patients were characterized clinically by twenty-three parameters (clinical, laboratory, instrumental).

Results: The local levels of IL-17A in RA patients were higher than the systemic concentrations (8.65±2.98 vs. 0.32±0.06 pg/ml, p=0.012). The ROC curve analysis for synovial IL-17A showed better performance than serum (AUC 0.885 (95% CI: [0.775÷0.995]), $p < 0.001$, vs. AUC 0.592, respectively). There was no significant

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difference in the serum IL-17A concentration among studied persons. Serum levels of IL-17A were higher in RA patients with mild activity comparedto those with moderate (p=0.028, p=0.008) and severe activity (p=0.069, p=0.037) determined by the disease activity index (DAS) 28 and the simplified disease activity index (SDAI), respectively. Serum levels of IL-17A correlated negatively with the presence of anemia (p=0.016). The SF levels of IL-17 were higher in patients with elevated ESR, CRP, presence of RF (IgM, IgG, IgA) and anti-CCP antibodies in the serum.

Conclusion: Our results confirmed the increased levels of IL-17A locally in RA which may play an essential role in the disease activity and progression. Serum concentrations of IL-17A could be used as a possible systemic biomarker for disease activity even in patients with mild disease activity scores or subclinical synovitis.

Keywords: Rheumatoid arthritis; Interleukin-17; Iinflamed synovial fluid; Disease activity; Biomarker.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune systemic disease arising from the interaction of genetic, epigenetic, and environmental factors (1). The disease is spread across all climate-geographic areas and affects 0.5 to 1% of the earth's population. It occurs two to three times more often in females and its frequency increases with age (2).The leading clinical symptomis erosive arthritis involving the peripheral joint, causes progressive articular damage and functional loss (1).There is an inflammation and hyperplasia of the synovial membrane, expansion of granulation tissue, and erosive and destructive changes in cartilage and underlying bone (1-3). The etiology of RA is not fully understood. However, the pathogenic changes that occur in the affected joint structures are studied in detail. Upon activation, fibroblast-like synoviocytes release cytokines and other mediators which are involved in the onset and maintenance of the inflammatory response. Therefore, it is shown that blocking of pro-inflammatory cytokines may control the activity of the disease. Some of these cytokines may also serve as biomarkers in managing RA patients (4). One has to have in mind that not all RA patients respond to current biologic therapies and responses are not always sustained, suggesting that there are alternative drivers of pathogenesis that might be promising therapeutic targets (5,6).

Studies from the last 20 years have shown that the IL-23–IL-17 axis is critically involved in the development of autoimmunity (7, 8).Th17 cells play a substantial role in the pathogenesis of some autoimmune diseases, including RA (8).According to one of the underlying assumptions about RA's etiopathogenesis, an infectious agent or its peptides found in the joints can induce the autoimmune process. Immediate activation of the IL-23 / IL-17 cascade, in which IL-23 maintains Th17 lymphocytes, leads to the attraction of neutrophils which emit oxygen radicals and other inflammatory mediators directed against microbial invasion. Moreover, Th17 cells are increased in the peripheral blood, and in synovial tissues and the SF of RA patients, even those at a nearly stage and treatment-naïve (5). It has been shown that Th17 and IL-17 play an important complex role in the pathogenesis of RA, including the occurrence of erosive joint changes (7). However, there is lack of investigations regarding the implication of IL-17 in the clinical context and practice. The roles of Th17 cells and IL-17 at different stages in the

development and progression of RA needs further investigation, including their implication in the diagnostic process or patients follow up.

Traditionally, the evaluation of disease activity and therapy monitoring in RA patients is based on the use of non-specific systemic inflammatory markers. Therefore, cases of subclinical synovial inflammation and low disease activity are often underestimated. This raises the need to identify biomarkers that directly reflect the extent and activity of synovial inflammation and are readily applicable in everyday clinical practice. Highly sensitive but non-specific laboratory parameters to assess inflammatory or immunological activity are widely used as markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement fractions, etc. (9). Diagnostic values for RA have the specific autoantibodies to cyclic citrullinated peptides – anti-CCP antibodies (9). The ideal biomarker would reflect and measure the severity of disease and joint damage in RA and would have a practical benefit in the clinical practice for predicting the course and the progress of the disease (10).

The aim of the study was to investigate the systemic and local levels of IL-17A in a Bulgarian cohort of RA patients compared to patients with inflammatory osteoarthritis (OA) and HCs. We studied the role of IL-17A as a biomarker for disease activity and severity by evaluating the relationship of the cytokine level and some clinical, instrumental, laboratory and immunological findings of the RA patients.

PATIENTS AND METHODS

Subjects of the study

Fifty-one persons were recruited in our study as follows: 20 with RA (39.2%) at mean age 48.5±15.7 years, 15 OA patients (29.4%) at mean age 65.9±14.5 years, and 16 HCs (31.4%) at mean age 35.4±9.2 years. Females were 41 (80.4%) and males – 10 (19.6%) of the patients

The diagnosis of RA patients was obtained after correct interpretation of the clinical picture, the results of the laboratory and instrumental examinationsaccording to the American College of Rheumatology (1987) (ACR) diagnosticcriteria for RA (11).

The OA patients fulfilled the American College of Rheumatology (ACR) classification criteria for diagnosis (12).

Selection of patients and HCs for the study was performed in the Clinic of Rheumatology, University Hospital St. Ivan Rilski, Sofia, according to the relevant inclusion and exclusion criteria. The inclusion criteria were as followed: people able to understand and agree to give informed consent to participate in the project; age between 18-70 years old; confirmed diagnosis of RA according tothe ACRdiagnosticcriteria for RA from 1987; active RA, defined by the Disease Activity Score (DAS28) $\geq$ 2.6; or confirmed diagnosis of OA according to the ACR classification criteria for OA; or HCs willing to participate in the study.The exclusion criteria covered the following but not limited to: persons with cognitive and mental disorders;persons under the age of 18 and over 70; persons with malignant disease and / or acute / chronic infection;persons with severe chronic illnesses - decompensated diabetes mellitus, chronic renal failure, chronic heart failure III-IV class of the New York Heart Association (NYHA), hepatic insufficiency.

All study subjects gave written consent for participation in the study approved by the Ethic Committee of the Medical University of Sofia and the research was performed according to the local hospitals` ethical considerations.

Characteristics of RA patients

According to the disease duration, RA patients were divided into three groups: 0-6 months (one patient), 7-24 months (five patients) and >24 months (fourteen patients). We used three disease activity indicators: the Disease Activity Score for 28 joints (DAS28) (2.6 – 3.2 mild; 3.2 - 5.1 moderate; >5.1 severe); the simplified disease activity index (SDAI) (3.4 - 11 mild; 11.1 - 26 moderate; 26.1 - 86 severe);and clinical disease activity index (CDAI) (2.9 - 10 mild; 10.1 - 22 moderate; 22.1 - 76 severe).The DAS28 score considers twenty-eight tender and swollen joint counts, general health, patient assessment of disease activity (by visual analogue scale (VAS) from 0 to100), levels of an acute phase reactant (i.e., ESR).

RA patients were subjected to the following laboratory investigations: complete blood count, erythrocyte sedimentation rate (ESR) mm/h, C-reactive protein (CRP). The immunological testing included testing for: anti-nuclear antibodies (ANA) (Indirect immunofluorescence, ANA-Hep2, Biosystems, Spain), serum rheumatoid factor (RF) (latex agglutination, Human, Germany), RF-IgG/IgM/IgA (Alegria ELISA, Orgentec, Germany), serum anti-CCP IgG/IgA (anti-CCP3) antibodies (ELISA, Quanta Lite CCP version 3.1, Inova Diagnostics, San Diego, CA).

The presence of synovitis was demonstrated bya positive Doppler signal on musculoskeletal ultrasound (MSUS) examination US Doppler. Synovial hypertrophy, when presented, was scored as mild, moderate or severe.

The studied RA patients were newly-diagnosed without therapy, or under disease modifying anti-rheumatic drugs (DMARDs), low dose corticosteroids and/or NSAIDs.

Specimens' collection and preparation

Five milliliters (ml) of peripheral venous blood from totally fifty-one subjects were collected in sterile tubes (Vacutainer BD-Plymouth, UK, 5 mL) from all study subjects. Serum samples were separated and frozen at -80˚C before testing.

Matched SF samples were obtained from the swollen joints in RA patients during routine diagnostic procedures and frozen at -80˚C before testing.

Serum and SF samples were thawed entirely prior testing.

Enzyme immunoassay

The concentration of IL-17A was measured in serum and SF from twenty RA patients and in serum samples of fifteen OA patients and sixteen healthy subjects by IL-17A ELISA kit (Gene probe, Diaclone, France). The immunological testing for IL-17A was performed at the Laboratory of Clinical Immunology, University Hospital "St. Ivan Rilski", Sofia. Each sample was tested in duplicates according to the manufacturer`s instructions.

Statistical methods

The raw data were analyzed by the software package for statistical analysis (SPSS®, IBM 2009), version 19. A parametric (paired and unpaired T-test, ANOVA) and non-parametric tests (Mann-Whitney) were used for analysis as well as a correlation studies. The results were accepted for significant if p value was less than 0.05.

RESULTS

The average serum levels of IL-17A showed similarity among different study groups: RA patients (0.32±0.27 pg/ml), OA patients (0.35±0.10 pg/ml) and HCs (0.66±0.20 pg/ml) (p=0.131) (Figure 1).Nevertheless, the local levels of IL-17A in RA patients were higher than the systemic concentrations (8.65±2.98 vs. 0.32±0.06 pg/ml, p=0.012) (Figure 2). ROC curve analysis revealed that the synovial IL-17A showed excellent performance (AUC=0.885, 95% CI [0.775 ÷ 0.995], p<0.001), compared to the serum levels (AUC=0.592 [0.303-0.700], p=0.987) (Figure 3).

Figure 1: Serum levels of IL-17 in RA, OA patients and healthy controls.

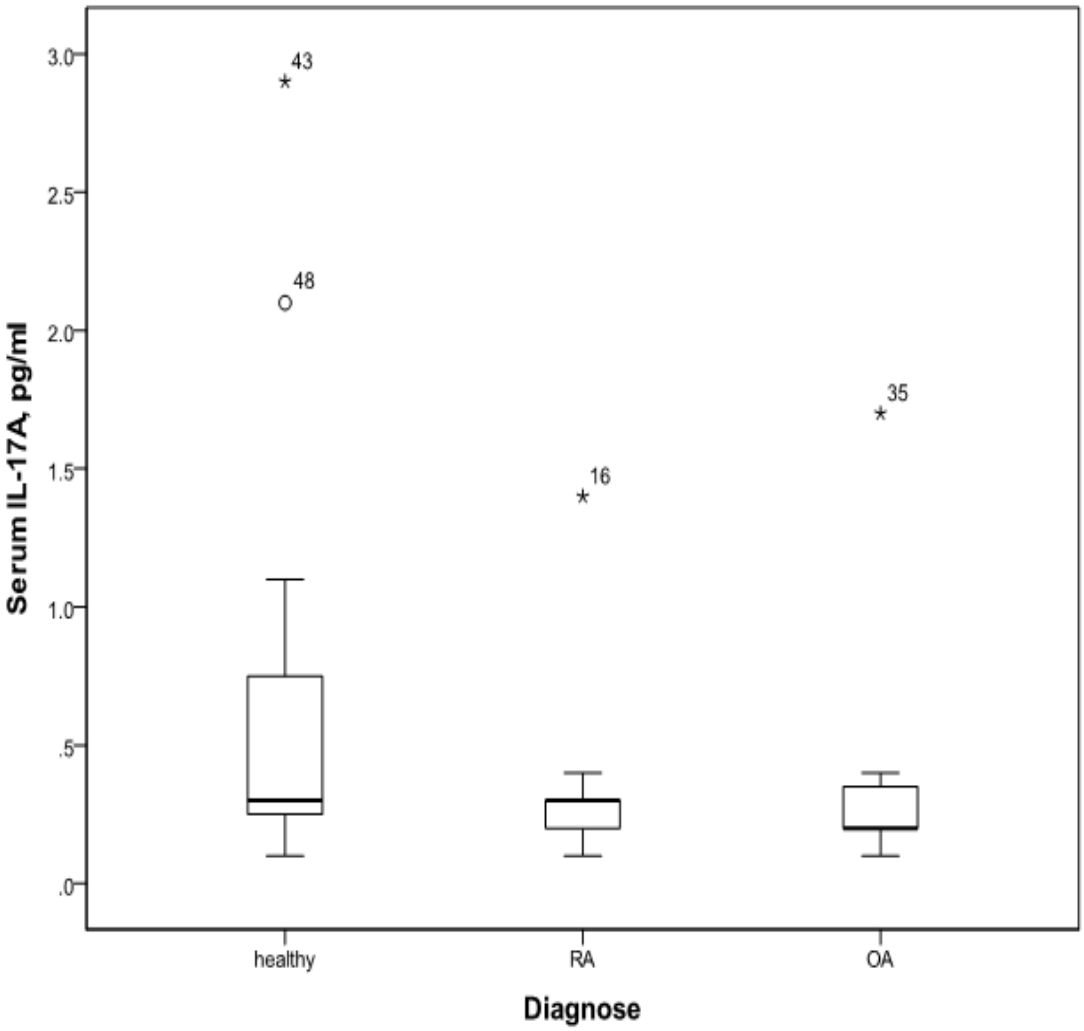

Figure 2: Serum and synovial levels of IL-17 in RA patients.

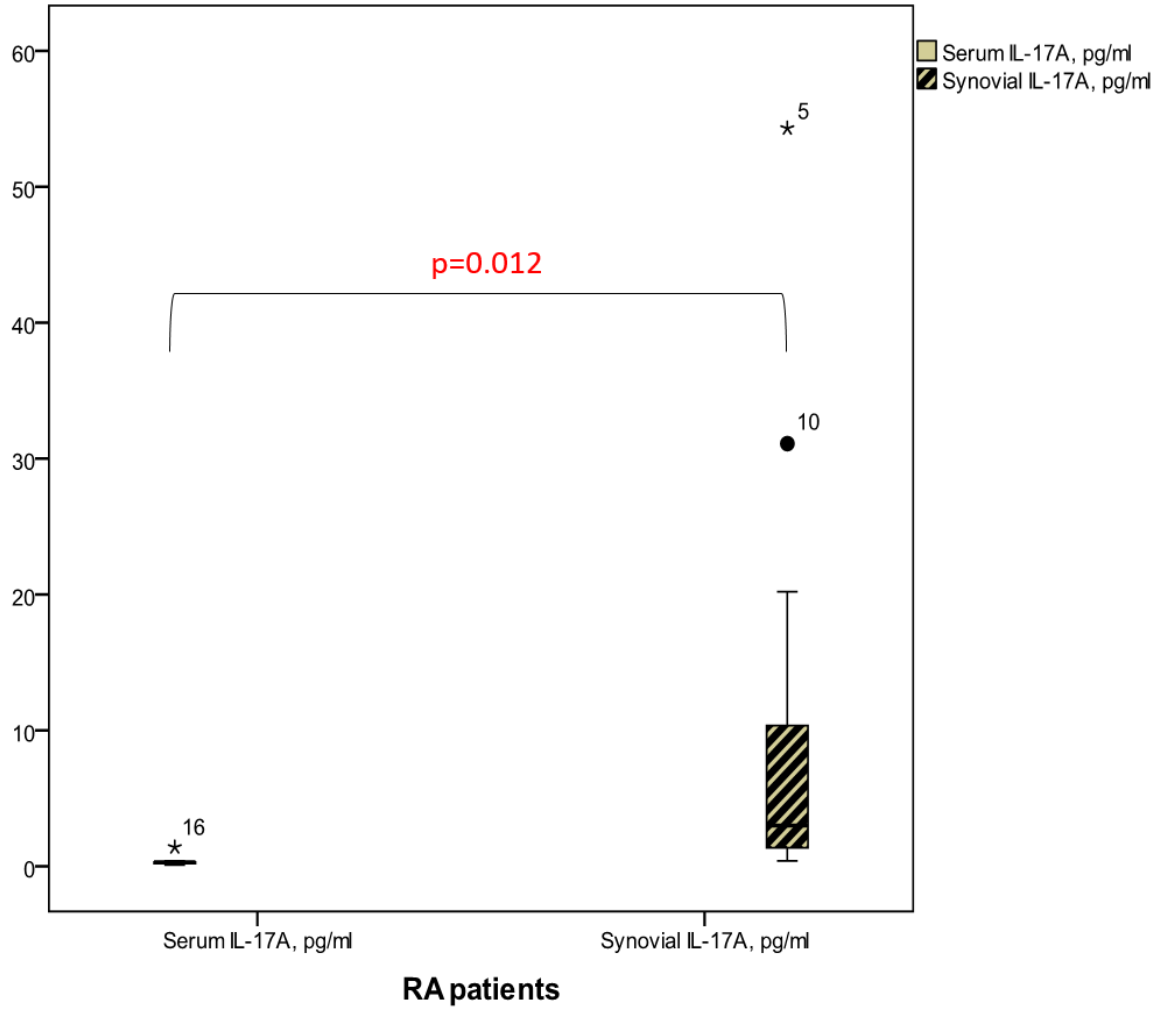

Table 1 represents serum and synovial levels of IL-17A in RA patients depending on clinical and laboratory findings. We found that the synovial levels of IL-17A were about 10-fold higher in patients with the duration of the disease 7÷24 and above 24 months, and 2-3-fold higher in patients with morning stiffness above 60 minutes. However, these results remained non-significant (Table 1).

According to disease activity scores, we obtained higher serum IL-17A level in RA patients with mild activity than those with moderate activity ($p = 0.028$) and compared to those with severe activity ($p = 0.069$), assessed by DAS28 (Figure 4A) (T-test analysis). We found greater serum level of IL-17A in RA patients with mild than moderate activity ($p = 0.008$) and moderate compared to severe activity ($p = 0.037$), assessed by SDAI (Figure 5A). We did not find alterations in serum or SFIL-17A concentrations depending on the disease activity, determined by CDAI. However, the synovial concentration of IL-17 increased simultaneously with the increase of all three disease activity scores (Table 1).

Figure 3: Receiver operating characteristic (ROC) curve analysis for IL-17A in serum and in synovial fluid in patients with RA.

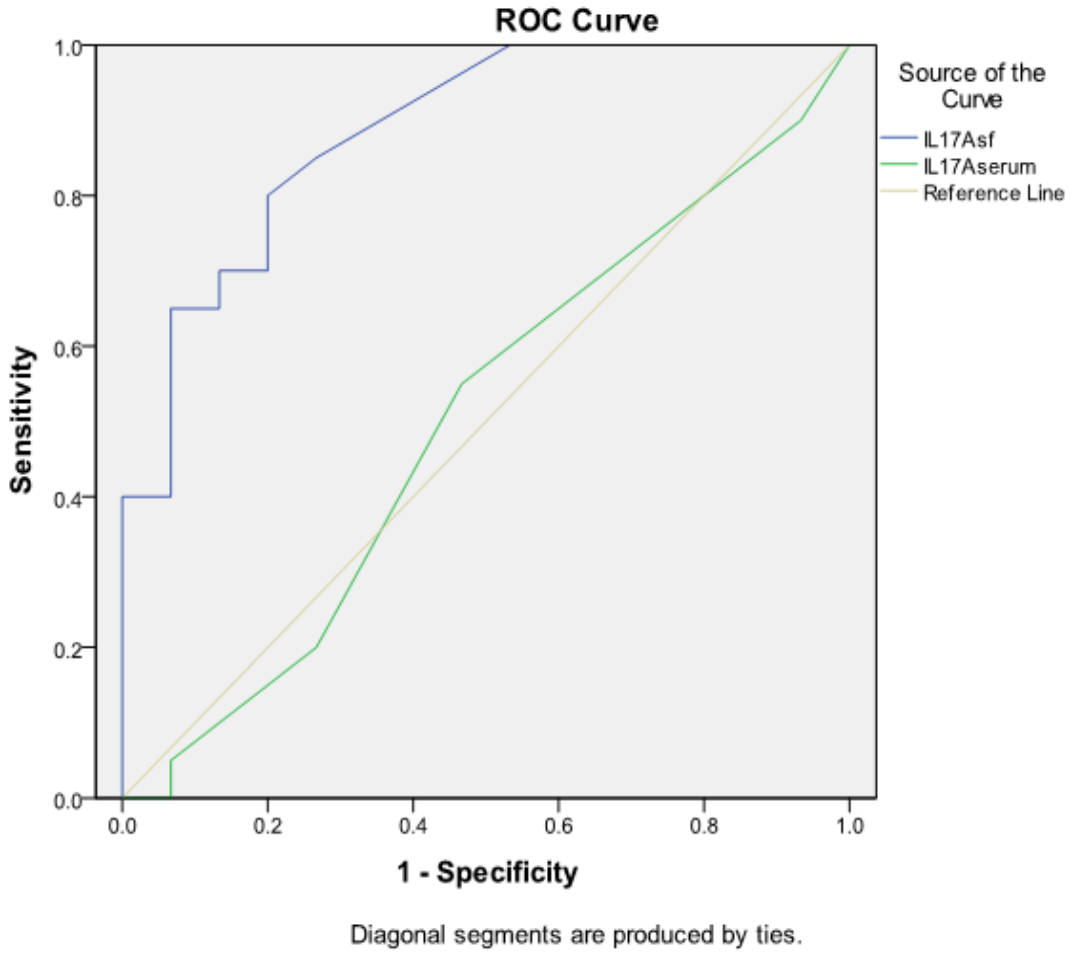

Figure 4: Serum (A) and synovial (B) levels of IL-17A in RA patients according to DAS28.

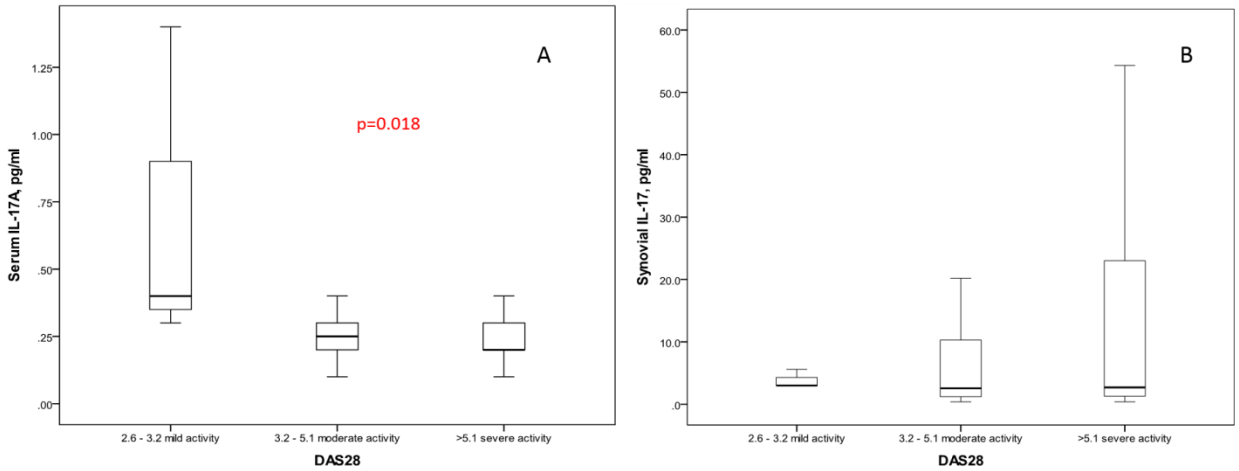

Figure 5: Serum (A) and synovial (B) levels of IL-17A in RA patients according to SDAI.

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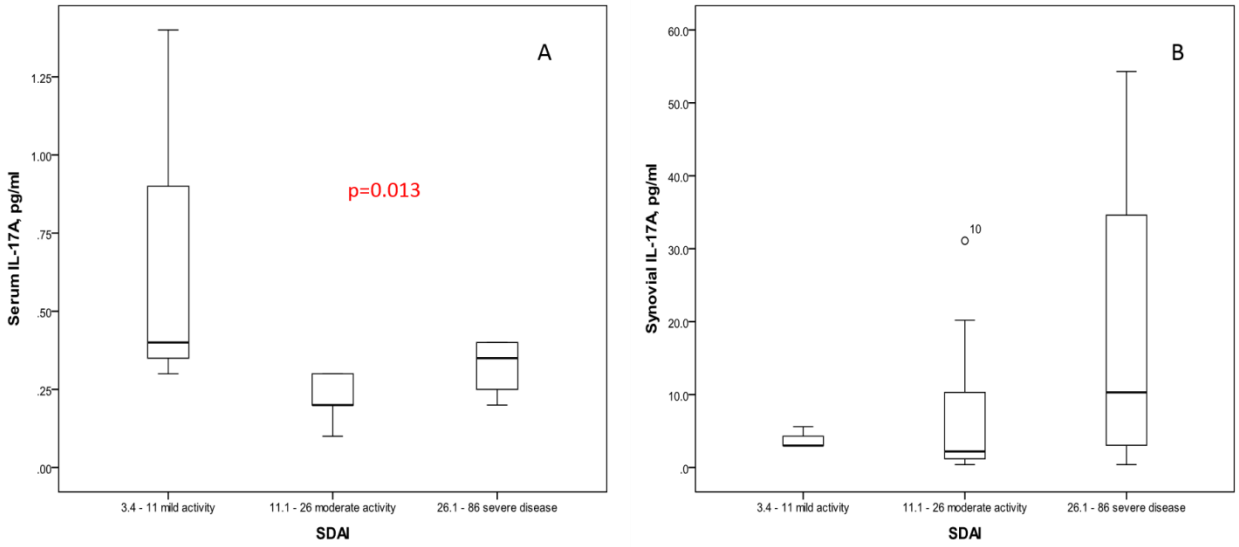


RA patients with higher serum IL-17A levels had also elevated ESR, anemia (p=0.066), presence of rheumatoid factors IgG, IgM and IgA (p>0.05) in the serum. Conversely, RA patients with lower serum concentrations of IL-17A showed normal CRP level (p=0.081), leukocytosis, absence of anti-nuclear (ANA) and anti-CCP antibodies (p>0.05). Although not significant, the SF levels of IL-17 were higher in patients with elevated ESR, CRP, RF (IgM, IgG, IgA) and anti-CCP at least 2-3 times (Table 1).

Regarding the SF concentrations of IL-17A in RA patients, we found that the levels increased in patients with synovitis, without reaching significance (Table 1). RA patients with synovial hypertrophy also displayed up-regulated levels. The third degreeofsynovitisassessed by Doppler was associated with the highest level of SF IL-17A (p=0.326).

Patients on corticosteroids and/ordisease-modifying drugs were with lower serum levels of IL-17A. Moreover, their local IL-17 concentrations were 2-3-times lower compared to levels in RA patients without therapy (Table 1).

We also found that the serum level of IL-17A correlated inversely with the concentration of hemoglobin (r = -0.532, p = 0.016) (Figure 6).

Table 1: Serum and synovial levels of IL-17A depending on some clinical and laboratory findings. Results are presented as mean±SE.

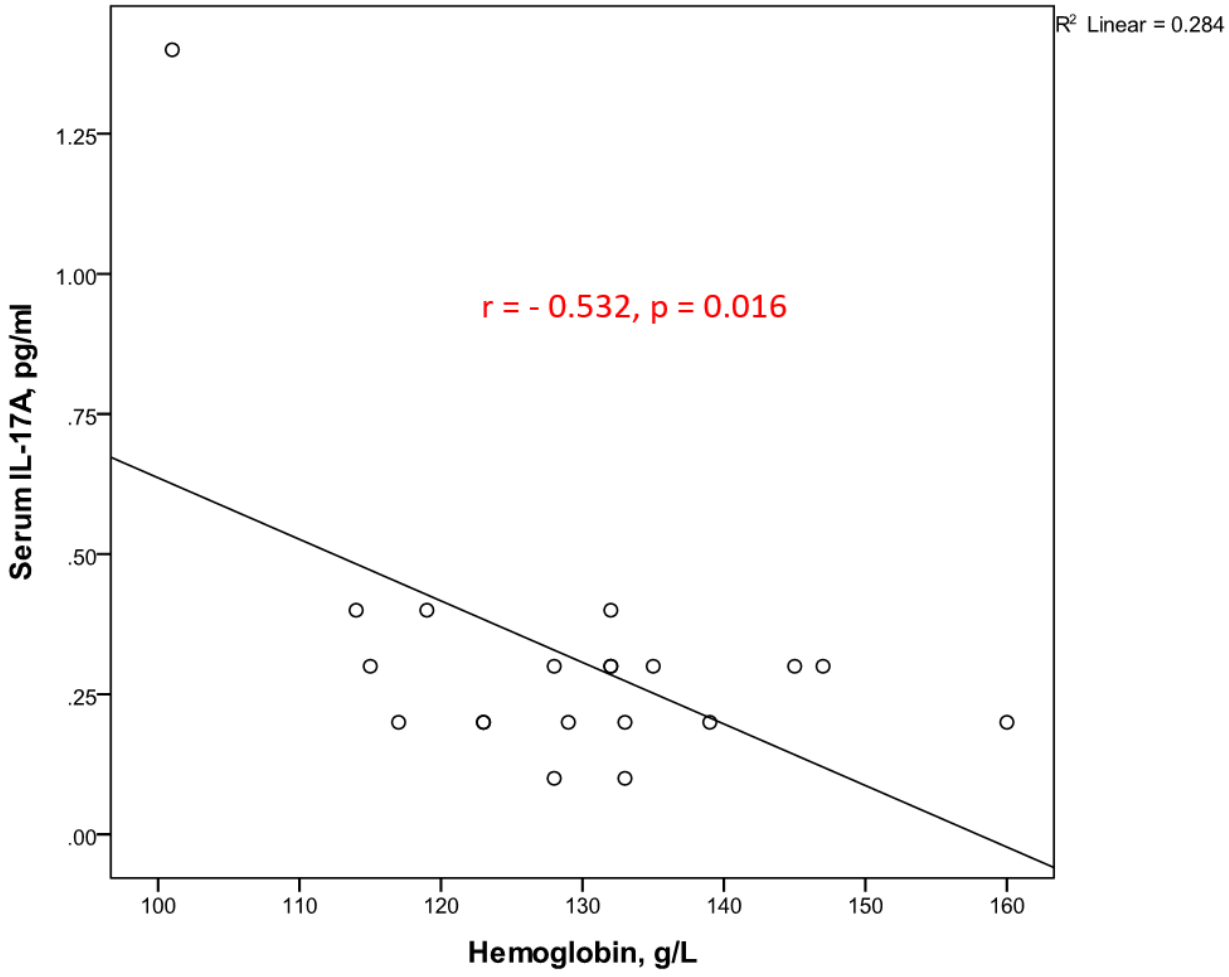
Characteristics of RA patients		**Serum IL-17**, pg/ml	Significance, p*	**Synovial IL-17**, pg/ml	Significance, p*
Cigarette smoking	Yes	0.28±0.03	0.741	12.93±8.38	0.360
	No	0.32±0.09		6.81±2.48	
Duration of the disease	0 - 6 months	0.20±0.05	0.212	0.40±0.06	0.827
	7 - 24 months	0.50±0.22		9.74±5.56	
	> 24 months	0.26±0.03		8.84±3.84	

Morning stiffness	0 – 30 min	0.55±0.29		7.95±4.13	
	30 – 60 min	0.26±0.02	0.149	5.97±2.75	0.469
	> 60 min	0.24±0.05		15.08±10.13	
Disease activity, DAS28	2.6 – 3.2 mild activity	0.70±0.35		3.87±0.87	
	3.2 - 5.1 moderate activity	0.25±0.03	0.018	5.53±2.02	0.287
	>5.1 severe activity	0.24±0.04		14.14±7.78	
Disease activity, CDAI	2.9 - 10 mild activity	0.58±0.28		3.28±0.28	
	10.1 - 22 moderate activity	0.24±0.03	0.090	7.48±2.72	0.301
	22.1 - 76 severe disease	0.28±0.05		17.50±12.73	
Disease activity, SDAI	3.4 - 11 mild activity	0.70±0.35		3.87±0.87	
	11.1 - 26 moderate activity	0.22±0.02	0.013	6.62±2.60	0.230
	26.1 - 86 severe disease	0.33±0.05		18.83±12.20	
ESR, mm/h	Normal	0.30±0.01	0.956	3.30±0.5	0.676
	Higher	0.32±0.06		13.63±3.13	
CRP, mg/dl	Normal	0.53±0.29	0.081	1.90±0.66	0.269
	Higher	0.26±0.02		10.33±3.62	
Synovitis	Yes	0.34±0.07	0.439	8.74±3.41	0.945
	No	0.20±0.06		8.13±6.06	
Doppler assessment of synovitis	No synovitis	0.20±0.06	0.267	8.13±6.05	0.623
	First degree	0.55±0.28		6.03±2.55	
	Second degree	0.25±0.03		5.75±3.67	
	Third degree	0.30±0.04		15.68±9.96	
Synovial hyperthrophy	No	0.20±0.03	0.326	5.26±3.76	0.876
	Mild	0.48±0.19		10.45±4.37	
	Moderate	0.25±0.04		11.10±8.68	
	Severe	0.30±0.06		5.77±4.59	
Anemia	Yes	0.48±0.19	0.066	5.78±2.38	0.544
	No	0.24±0.02		9.87±4.15	
Leukocytosis	Yes	0.30±0.06	0.920	8.53±4.28	0.988
	No	3.18±0.71		8.67±3.47	
Anti-nuclear antibodies	Negative	0.32±0.70	0.746	9.85±3.43	0.348
	Positive, ≥1:80	0.27±0.03		1.80±0.75	
Rheumatoid factor IgM, IU/ml	Negative	0.23±0.05	0.471	2.33±0.61	0.302
	Positive	0.34±0.07		10.23±3.64	
Rheumatoid factor IgG, IU/ml	Negative	0.22±0.04	0.378	1.94±0.61	0.202
	Positive	0.35±0.08		10.88±3.82	

Rheumatoid factor IgA, IU/ml	Negative	0.22±0.04	0.378	1.94±0.61	0.202
	Positive	0.35±0.08		10.88±3.82	
Anti-CCP, IU/ml	Negative	0.39±0.15	0.340	3.74±1.63	0.186
	Positive	0.27±0.03		11.97±4.69	
Corticosteroids	Yes	0.27±0.04	0.614	2.33±1.06	0.172
	No	0.34±0.08		11.35±4.06	
Disease modifying drugs	Yes	0.26±0.02	0.612	3.48±1.83	0.330
	No	0.33±0.08		10.37±3.86	

*Assessed by ANOVA analysis.

Figure 6: Correlations between serum levels of IL-17A and hemoglobin.



DISCUSSION

We aimed to investigate systemic and local levels of IL-17A in RA patients and to ascertain the role of IL-17A as a biomarker for disease activity and severity by evaluating the relationship of the cytokine level and some clinical, laboratory and immunological findings of the RA patients. Although we did not establish a difference in serum levels of IL-17A betweenthe study groups (0.32±0.27 vs. 0.35±0.10 vs. 0.66±0.20 pg/ml in RA, OA, and HCs respectively), we found significantly higher concentration of IL-17A in the SF than serum of RA patients (8.65±2.98 vs. 0.32±0.06 pg/ml, p=0.012). Moreover, ROC curve analysis revealed that the SF IL-17A was superior to the serum concentrations for diagnosis in RA patients (AUC=0.885 vs. AUC=0.592).

Other studies, however, documented substantial differences in the percentage of Th17 cells and serum levels of IL-17 of RA patients compared to controls (4.62±1.13% and 204.1±33.8 pg/ml, respectively, p<0.001) (13) and 5-foldincreased IL-17 compared to the control (14). It has also been suggested that the Th17/Treg imbalance along with enhanced IL-17 may be responsible for the progression of RA (14).

There are some studies that haveinvestigated the relationship between IL-17A and disease activity. A recent survey on Egyptian RA patients did not finds a correlation between serum IL-17A and DAS28. However, they observed significantly higher serum IL-17A in severely active patients as compared to patients with moderate activity (15).In our study; we found significant correlations between serum IL-17A and the disease activity, assessed by DAS28 and SDAI, but not with CDAI. Surprisingly, we observed higher serum levels of IL-17A in patients with mild activity, evaluated by all three used scores. This observation makes us speculating that the serum IL-17A is up-regulated even in early RA and could be employed in the diagnostic process of subclinical arthritis. Lubberts et al. also determined the role of Th17 and Th1 lymphocytes in early and established RA (7).

Other authors found significant correlations between serum levels of IL-17 and DAS-28, along with some laboratory findings (ESR, CRP, TNF-a) and clinical characteristics of RA patients (MRI score of synovitis, MRI erosions for joint destruction, tender joint count, swollen joint count) (13,16-18). We have also found some associations of serum IL-17A and CRP and the presence of anemia (borderline significance, p=0.081 and 0.066, respectively). Unfortunately, we did not find asignificant difference in IL-17A levels and established immunological RA-related parameters, i.e., RF and anti-CCP antibodies levels. High concentrations of IL-17A in both blood and SF were associated with disease severity in RA and with disease biomarkers such as anti-CCP antibodies, suggesting elevated IL-17A signifies a more severe clinical course in RA (17,19-21).In our study, the SF concentration of IL-17 increased simultaneously with all the three disease activity scores, although non-significantly (Table 1). We also observed that the SF levels of IL-17 were higher in patients with elevated ESR, CRP, RF (IgM, IgG, and IgA) and anti-CCP at least 2-3 times. We believe that future investigation comprises of a larger sample size would clarify these trends.

Many studies demonstrate thatIL-17 is produced in the RA synovium which coincides with our results regarding up-regulated protein expression of IL-17A in synovial fluid (Figure 2). Previous studies demonstrated that synovial explants from RA patients, but not OA patients, are able to produce IL-17A ex vivo (20,22).The source of IL-17A in the synovium, is mainly Th17 cells, but a wide range of cells of the adaptive and innate immune systems,i.e.,CD8+T lymphocytes, gd T cells, NKT cells, NK cells, neutrophils, macrophages, eosinophils, mast

cells, could secretethis cytokine (5,23,24).The endogenous secretion of IL-17 from the cartilage appears unlikely (25).

It was shown that the administration of IL-17 into normal knee induced joint degradation (25). Moreover, this effect was observed using IL-17 alone which differs in vivo where several cytokines, such as IL-1, TNF-a,and IL-17, act together in inflamed joints (25).These observations led to the suggestion that IL-17 has a significant but unlikely a central role in the pathogenesis of RA (26).Several investigators have focused on the potential role ofIL-17 in mediating joint damage. Chabaud et al. (26) demonstrated the role of IL-17 in destruction and defective formation of cartilages and bones in RA. IL-17A was shown to act synergically with fibroblasts, synoviocytes, and T cells which express the activator of osteoclast formation – RANKL (27, 28). Milanovaet al. (2014) investigated the inflammatory and destructive potential of neutrophils in RA in zymosan-induced mouse models of arthritis. They found that neutrophils increased the processes of bone and cartilage joint destruction by RANKL expression and increased production of IL-17A (29).Other possible effects of IL-17 are the induction of matrix destruction in cartilage (30), collagen release from cartilage (31), inhibition of osteoblast differentiation and function (32),induction of chronic destructive arthritis in an IL-1and TNF independent way (33).In our study, RA patients with synovitis and synovial hypertrophy displayed up-regulated levels, especially third degree of synovitis.

IL-17A also has vascular effects, such as stimulation of neoangiogenesis and thrombosis in inflamed joints, production of angiogenic factors, migration of endothelial cells and tube formation.Although predominantly acting at the local site, IL-17A can circulate in the blood and thus may exert systemic effects, including induction of a pro-coagulant state (32), which combined with impaired micro vascular function and arterial compliance, may contribute to the enhanced cardiovascular risk associated with RA (5).

Locally, IL-17 recruits monocytes from peripheral blood to inflamed joints, where they differentiate into macrophages. The latter in conjunction with fibroblasts secretea large amount of pro-inflammatory cytokines. This supports inflammation and attracts neutrophils, which secrete more mediators and calprotectin (32). This massive cellular infiltration comprises T and B cells, macrophages, granulocytes, and dendriticcells is a primary feature of synovitis in RA. Abundant immune cells and pro-inflammatory cytokines and chemokines, eventually leading to the destruction of the joint and bone (34).Soon after these observation sit was found that SF of RA patients have highIL-17A levels compared to those with OA (34). However, we did not assess SF samples from OA patients.

Regarding therapy modalities of our RA patients, we observed slightly higher levels of serum IL-17A and 2-3-fold increased levels of synovial IL-17A in treatment naïve patients compared to those on corticosteroids or DMARDs, although without reaching significance. Some studies observed a significant association between IL-17A level and active RA disease among RA patients on non-biological therapy ($p=0.03$) (16).

The development of novel therapeutic agents - monoclonal antibodies directed against IL-17A,supplements the theoretical knowledge accumulated for the role of IL-17 in the pathogenesis of RA (43,65).In experimental models, overexpression of IL-17A could be blocked to inhibit joint inflammation, cartilage damage and bone erosion (20,35).

Several IL-17 blocking agents are in clinical trials for RA - secukinumab (AIN457), ixekizumab (LY2439821) and brodalumab (AMG-827) (5, 7, 32, 34, 36). An extensive meta-analysis of Kunwar et al. concludes

that anti-IL-17 antibodies are not only useful treatment for RA but also with acceptable safety profile, despite some limitation such as heterogeneity and small duration of studies (36). Moreover, the fluctuating effectiveness of biological therapies from patient to patient suggests the heterogeneity of RA regarding the particular cytokines contributing to disease development in different RA patients. Probably the distinct members of theIL-17 family may show high variability in the expression in individual patients which also influences the response to biologic therapy (37).Interestingly, the need for new therapies creates a niche for the development of entirely different treatment options, such as phytocompounds genistein and citral which show promising efficacy and greater activity than the other and traditional inhibitors against IL-17A and IL-D cytokines in RA and other autoimmune disorders (38).

CONCLUSION

Taken together, our results confirmed the increased levels of IL-17A locally in RA. The difference between the systemic and local concentration of IL-17A suggests that the local inflammatory milieu stimulates the production of IL-17A and the latter may play an essential role in the disease activity and progression. Serum concentrations of IL-17A could be used as a possible systemic biomarker for disease activity even in patients with mild disease activity scores or subclinical synovitis. However, larger sets are needed to confirm the diagnostic and prognostic accuracy of IL-17A in RA.

CONFLICT OF INTERESTS: None declared.

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