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Interaction between TNF inhibitors and serum IL-17 levels and susceptibility to rheumatoid arthritis

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ABSTRACT

This study aimed to assess the central role of the immunological marker interleukin-17 (IL-17) and to investigate the interaction between tumor necrosis factor (TNF) inhibitors and serum IL-17 levels in relation to susceptibility in patients with rheumatoid arthritis (RA). Serum samples were collected from three groups: patients with RA receiving TNF inhibitor therapy, patients with newly diagnosed (early) RA, and healthy controls. Serum IL-17 levels were measured using enzyme-linked immunosorbent assay (ELISA). Serum IL-17 concentrations were significantly higher in RA patients treated with TNF inhibitors compared with the other groups ($p < 0.001$). Based on the present findings, increased serum IL-17 levels in RA patients undergoing TNF inhibitor therapy may indicate a better response to anti-TNF treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease characterized by symmetric polyarthritis affecting both small and large joints, which may lead to joint and periarticular structural damage as well as systemic inflammation [1]. The disease affects women two to three times more frequently than men and can occur at any age. RA is associated with disability, reduced work capacity, and increased mortality [2].

Tumor necrosis factor (TNF)-α inhibitors, including etanercept, golimumab, adalimumab, infliximab, and certolizumab pegol, are biologic agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis and other autoimmune diseases [3]. TNF inhibitor (TNFi) therapy has revolutionized the management of RA in many patients by reducing synovial inflammation and preventing long-term structural damage to cartilage and bone [4].

Interleukin-17 (IL-17) is a pro-inflammatory cytokine that plays a critical role in the development of chronic inflammation associated with various conditions, including allergies, cancer, and autoimmune diseases such as rheumatoid arthritis. IL-17 is produced by multiple immune cell types from both the adaptive and innate immune systems, including T helper 17 (Th17) cells, $CD8^+$ T cells, natural killer T cells, and innate lymphoid cells [5].

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MATERIALS AND METHODS

Study design and participants

This cross-sectional study included 100 Iraqi patients diagnosed with rheumatoid arthritis (RA) who attended the Rheumatology Department of Al-Sadr Medical City in Najaf and the Rheumatology Unit of Murjan Medical City in Hilla. The study population was divided into two groups: 50 patients with newly diagnosed (early) RA and 50 patients with RA receiving tumor necrosis factor (TNF) inhibitor therapy.

Patient selection was based on clinical evaluation by rheumatologists in accordance with the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria, supported by serological investigations. The early RA group comprised 4 males and 46 females, whereas the TNF inhibitor-treated group included 11 males and 39 females. The age of participants ranged from 22 to 76 years.

Clinical assessment and data collection

Clinical and demographic data were collected by the rheumatologist and the researcher using a structured questionnaire, including age, sex, smoking status, family history of RA, and other relevant clinical information. Disease activity was assessed using the Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR). Based on DAS28-ESR values, disease activity was categorized as mild, moderate, or severe.

Sample collection and storage

Venous blood samples were collected from each participant into sterile gel tubes and centrifuged to separate the serum. The serum samples were aliquoted into Eppendorf tubes and stored at -20°C to -45°C until analysis.

Control group

A control group consisting of approximately 50 apparently healthy volunteers without a history of autoimmune or inflammatory diseases was also included in the study.

Measurement of serum IL-17 levels

Serum interleukin-17 (IL-17) concentrations were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, China), according to the manufacturer's instructions. The ELISA plates were pre-coated with human IL-17 – specific antibodies. IL-17 present in the serum samples bound to the immobilized antibodies, followed by the addition of biotinylated human IL-17 antibodies. Streptavidin – horseradish peroxidase (HRP) conjugate was then added. After washing to remove unbound components, a substrate solution was added, producing a colorimetric reaction proportional to the concentration of IL-17 in the samples. The reaction was stopped by the addition of an acidic stop solution, and absorbance was measured at 450 nm using a microplate reader.

RESULTS

Demographic characteristics

The demographic characteristics of patients with newly diagnosed rheumatoid arthritis (RA), RA patients receiving TNF inhibitor therapy, and healthy control subjects are presented in Table 1. The mean age of patients with newly diagnosed RA was 50.62 ± 11.00 years, compared with 47.92 ± 11.50 years in TNF inhibitor-treated RA patients and 46.42 ± 10.98 years in the control group. No statistically significant difference in mean age was observed among the three groups (p = 0.166). The distribution of age categories was also comparable between RA patients and healthy controls.

Table 1. Demographic characteristics of patients with rheumatoid arthritis and healthy controls

Characteristic	Early diagnosis with RA n=50	RA under treatment with TNF Inhibitors n=50	Control subjects n=50	p
Age (years)				
Mean ±SD	50.62± 11.00	47.92 ± 11.50	46.42 ± 10.98	0.166† NS
Range	23-76 years	22-70 years	23-69 years	
< 30, n (%)	2 (4.0 %)	4 (8.0 %)	6 (12.0 %)	0.447¥ NS
30-39, n (%)	4 (8.0 %)	7 (14.0 %)	9 (18.0 %)	
40-49, n (%)	15 (30.0 %)	17 (34.0 %)	14 (28.0 %)	
≥ 50, n (%)	29 (58.0 %)	22 (44.0 %)	21 (42.0 %)	
Gender				
Male, n (%)	4 (8.0 %)	11 (22.0 %)	4 (8.0 %)	0.052¥ NS
Female, n (%)	46 (92.0 %)	39 (78.0 %)	46 (92.0 %)	
Male: female ratio	1:11.5	1:3.5	1:11.5	

¥ - Chi square, † - independent t test

With respect to sex distribution, the newly diagnosed RA group consisted of 4 males (8.0%) and 46 females (92.0%), whereas the TNF inhibitor-treated RA group included 11 males (22.0%) and 39 females (78.0%). The control group comprised 4 males (8.0%) and 46 females (92.0%). No statistically significant difference in sex distribution was detected among the groups (p = 0.052). These findings indicate that the patient and control groups were adequately matched for age and sex. The sex distribution of the study population is illustrated in Figure 1.

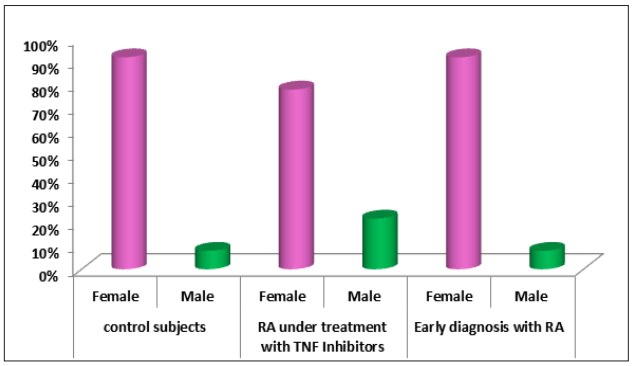

Figure 1. Distribution of patients and control subjects according to sex

Serum IL-17 levels

Serum interleukin-17 (IL-17) concentrations in patients and healthy controls are summarized in Table 2 and illustrated in Figure 2. The mean serum IL-17 levels were 1.84 ± 0.25 in patients with newly diagnosed RA, 2.07 ± 0.35 in RA patients receiving TNF inhibitor therapy, and 1.85 ± 0.37 in healthy controls. Serum IL-17 concentrations were significantly higher in RA patients treated with TNF inhibitors compared with both newly diagnosed RA patients and healthy controls (p < 0.001). No significant difference was observed between the newly diagnosed RA group and the control group.

Table 2. Serum interleukin-17 (IL-17) levels in patients with rheumatoid arthritis and healthy controls

Characteristic	Early diagnosis with RA n=50	RA under treatment with TNF Inhibitors n=50	Control subjects n=50	p
IL-17				
Mean± SD	1.84±0.25^{A}	2.07±0.35^{B}	1.85±0.37^{A}	0.001† HS
Range	1.49–2.43	1.22–2.6	1.27–2.66	

Different letters indicate important differences at p < 0.05
† - independent t test

Correlation analysis

The correlations between serum IL-17 levels and inflammatory markers in RA patients are shown in Table 3. In patients with newly diagnosed RA, serum IL-17 levels were positively correlated with C-reactive protein (CRP) (r = 0.373, p = 0.008). In contrast, in RA patients receiving TNF inhibitor therapy, serum IL-17 levels showed a significant negative correlation with anti-cyclic citrullinated peptide (anti-CCP) antibodies (r = −0.374, p = 0.007). No statistically significant correlations were observed

between IL-17 levels and rheumatoid factor (RF) or erythrocyte sedimentation rate (ESR) in either group.

Table 3. Correlation between serum IL-17 levels and inflammatory markers (CRP, RF, ESR, and anti-CCP)

Characteristic	IL-17			
	Early diagnosis with RA		RA under treatment with TNF Inhibitors	
	R	P	R	P
CRP	0.373*	0.008	0.101	0.285
RF	-0.017	0.909	0.022	0.878
ESR	-0.217	0.130	0.074	0.612
anti-CCP	0.087	0.547	-0.374*	0.007

r - correlation coefficient, * - significant correlation

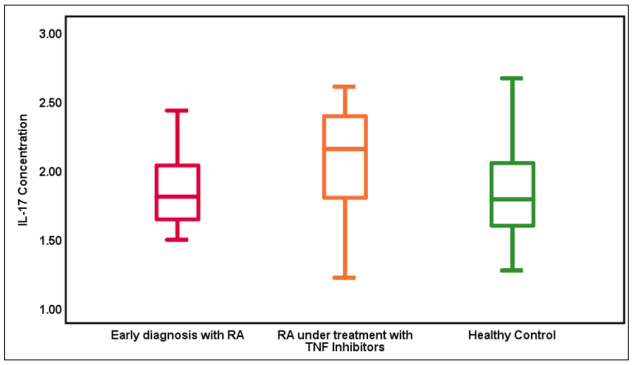

Figure 2. Box plot comparing serum IL-17 levels among patients with rheumatoid arthritis and healthy controls

DISCUSSION

Rheumatoid arthritis (RA) can affect individuals at any age; however, it is more frequently observed in people over 50 years of age [6]. In the present study, the mean age of patients with newly diagnosed RA was 50.62 ± 11.00 years, whereas the mean age of RA patients receiving TNF inhibitor therapy was 47.92 ± 11.50 years. The overall mean age of the patient group was 48.17 ± 11.23 years, compared with 46.42 ± 10.98 years in the healthy control group. No statistically significant difference in mean age was observed between patients and controls ($p = 0.166$). These findings are consistent with those reported by [7], who found a mean age of 48.56 years in RA patients and 43.05 years in controls, with no statistically significant difference between groups ($p > 0.01$) [8].

RA is known to affect women more frequently than men, with an approximate female-to-male ratio of 2:1 [6]. In the present study, females constituted the majority of participants in both RA groups. Specifically, the newly diagnosed RA group comprised 92.0% females, while the TNF inhibitor-treated RA group included 78.0% females. Similarly, females accounted for 92.0% of the control group. Although no statistically significant difference in sex distribution was observed between patients and controls ($p = 0.052$), the predominance of females among RA patients supports the established association between female sex and RA susceptibility. These results are in agreement with previous studies reporting a significantly higher prevalence of RA among females compared with males [9], and are slightly higher than the female proportions reported in other populations [10,11].

Regarding serum interleukin-17 (IL-17) levels, the present study demonstrated no significant difference between patients with newly diagnosed RA and healthy controls (1.84 ± 0.25 vs. 1.85 ± 0.37). These findings are consistent with those of [12], who reported no significant difference in serum IL-17 and TNF-α levels between RA patients and controls, as well as with previous studies indicating comparable IL-17 levels in the serum and synovial compartments of RA patients and healthy individuals [13,14].

In contrast, serum IL-17 levels were significantly higher in RA patients receiving TNF inhibitor therapy compared with newly diagnosed RA patients (2.07 ± 0.35 vs. 1.84 ± 0.25). This observation is consistent with the findings of [15], who reported that higher IL-17A levels may predict a favorable response to anti-TNF therapy. However, these results are not universally supported, as other studies have shown no significant changes in serum IL-17A levels following anti-TNF treatment [16], while some investigators have reported that increased circulating Th17 cells and elevated IL-17 levels are associated with a poor response to TNF inhibitor therapy [17]. These discrepancies may be attributed to differences in study design, disease duration, treatment regimens, and sample size.

Correlation analysis revealed a significant positive association between serum IL-17 levels and C-reactive protein (CRP) in patients with newly diagnosed RA, suggesting a link between IL-17–mediated inflammation and systemic inflammatory activity. In contrast, a significant negative correlation was observed between IL-17 levels and anti–cyclic citrullinated peptide (anti-CCP) antibodies in RA patients receiving TNF inhibitor therapy. Similar associations between IL-17 and inflammatory markers, including CRP and ESR, have been reported previously [12,18], supporting the role of IL-17 as an important mediator of inflammatory activity in RA.

CONCLUSION

Based on the present study, increased serum IL-17 levels in patients with rheumatoid arthritis receiving TNF inhibitor therapy suggest that higher IL-17A concentrations may predict a favorable response to anti-TNF treatment.

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