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Serum Markers Predicting Early Non-Responsiveness to Infliximab in Rheumatoid Arthritis: Tumor Necrosis Factor (TNF)-Alpha, TNFRII, and Interleukin (IL)-17 As Potential Indicators

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Abstract

Background Infliximab is a type of biologic medication used in the treatment of rheumatoid arthritis (RA) and other autoimmune conditions. While it can be highly effective for many patients, there are cases of early unresponsiveness to infliximab.

Objective To investigate the predictive value of serum biomarkers, specifically tumor necrosis factor alpha TNF-α), TNFRII, and interleuking-17 (IL-17), in identifying early non-responsiveness to infliximab in patients with RA.

Methods In this case-control study blood samples were obtained from 100 RA patients (50 responders and 50 non-responders) and 100 age and sex matched apparently healthy control. Serum levels of TNF-α, TNFRII, and IL-17 were measured by enzyme-linked immunosorbent assay.

Results In patient group, the median serum level of (TNF-α and IL-17) were higher than those of control group with a significant difference. Additionally, the median serum levels of TNF-α, and IL-17 in non-responder patients were significantly higher than those in responder group. Although, there was a higher median level of TNFRII in non-responder patients, no significant differences were observed. TNFRII displayed a significant positive correlation with TNF-α. While IL-17 had a significant positive correlation with each of TNFRII and TNF-α. ROC test revealed that TNF-α had 81% sensitivity and 74% specificity at a cut-off value of 78.4 ng/l, while TNFRII had 80% sensitivity and 77% specificity at 7.8 ng/ml, and IL-17 had 80% sensitivity and 71% specificity at a cut-off value of 46.91 ng/l.

Conclusion There was a positive association between elevated levels of TNF-α and IL-17 and early unresponsiveness to infliximab in RA patients.

Keywords Rheumatoid Arthritis, TNF-α, TNFRII, IL-17.

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List of abbreviations: CDAI = Clinical disease activity index, CRP = C-reactive protein, ELISA = Enzyme-linked immunosorbent assay, TH17 = T helper 17 cells

Introduction

Tumor necrosis factor alpha (TNF-α) is a cytokine with diverse effects on different types of cells. Its role as a

major regulator of inflammatory responses has been well established, and it is known to play a significant role in the pathogenesis of various inflammatory and autoimmune diseases [1]. In the context of rheumatoid arthritis (RA), TNF-α is particularly important as it is considered the primary inflammatory cytokine involved in the development and progression of the disease [2]. The TNF receptor superfamily (TNFRSF) is a group of proteins that function as cytokine receptors. They possess a specific ability to bind TNF through an extracellular cysteine-rich domain. This binding interaction is critical for transmitting the signals that TNF-α conveys to its target cells, which in turn can influence various physiological processes, including inflammation [3].

Interleukin-17 (IL-17) is a pro-inflammatory cytokine that holds significant importance in the development and progression of numerous chronic inflammatory and autoimmune diseases. IL-17 signaling can have a profound impact on controlling the pathogenesis of these disorders [4].

TNF inhibitors (TNFi) represent the first line of biological agents used in the treatment of RA and continue to be commonly prescribed for patients who do not adequately respond to conventional disease-modifying antirheumatic drugs (conventional synthetic disease-modifying anti-rheumatic drugs). Also, it has been observed that approximately one-third of RA patients do not achieve sufficient improvement with TNFi therapy [5,6].

When assessing the treatment response to biologic and targeted synthetic disease-modifying antirheumatic drugs in RA patients, the classification is divided into primary and secondary non-response, depending on the evidence of an initial response. Primary non-response is typically determined when there is no clinical improvement during the initial treatment period, indicating that the drug was ineffective from the beginning. On the other hand, secondary non-response is characterized by a loss of effectiveness over time, even after an initial response. It is important to note that the mechanisms underlying primary and secondary non-response may vary [7-9]. Thus, defining the type of non-response is the key to improving patient care.

By analyzing these biomarkers (TNF-α, TNFRII and IL-17), this study aimed to identify the association between the initial therapeutic response to infliximab with serum level of the above biomarkers ultimately enhancing the understanding of early unresponsiveness in RA patients.

Methods

A group of 100 patients with RA under the treatment with TNF-α inhibitor (infliximab) after ≤6 months duration was enrolled in this case-control study. They were collected from the unit of Rheumatology in Baghdad Teaching Hospital and Al-Yarmouk Teaching Hospital from January 2021 to September 2021. Each case in the study was diagnosed by a qualified rheumatologist and confirmed through laboratory investigations. The classification of the cases was based on the criteria set by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) in 2010 [10].

To establish a baseline for comparison, a control group comprising 100 individuals who were similar in terms of age and sex and appeared to be in good health was also included in the study.

To ensure ethical standards were met, the study obtained ethical approval and informed consent from each participant following the guidelines outlined in the declaration of Helsinki. The Institutional Review Board (IRB) provided the necessary ethical agreement for the study in College of Medicine, Al-Nahrain University under the number 20211045 in 2021.

Venous blood was collected from both patients and controls. Two ml of blood were collected in gel tubes to obtain serum for analysis. The levels of TNF-α, TNFRII, and IL-17 in the serum were measured using enzyme-linked immunosorbent assay (ELISA) kits provided by

Bioassay Technology Laboratory/China were utilized. The assay was conducted following the instructions provided by the manufacturer to accurately quantify the levels of TNF-α, TNFRII, and IL-17 in the serum samples.

To assess the clinical disease activity, the Clinical Disease Activity Index (CDAI) was calculated using the Rhumahlper application. The patients were categorized into different clinical subgroups based on their CDAI scores, following the criteria established by EULAR [11]. Treatment response was evaluated and classified according to the EULAR response criteria (Table 1).

Table 1. Treatment response according to EULAR criteria

EULAR response criteria	Interpretation
CDAI <10	Responders
CDAI >10	Non-responders

Statistical Analysis

The statistical analyses were conducted using statistical package for social sciences software version 25.0 from SPSS, Chicago. Categorical variables were presented as numbers and percentages and analyzed using the Chi-square test. Receiver operating characteristic curve (ROC) was used to evaluate the diagnostic value of TNF-α, TNFRII, and IL-17 in the context of discrimination between patients and the control group. Spearman's correlation test was used to explore the possible correlation that present between (TNF-α, TNFRII and IL-17) with other continuous variables as well as between each other. A P value less than 0.05 was considered to indicate a statistically significant difference.

Results

Demographic Characteristics of the study population

The mean age of the patients was 46.22±11.33 years which was nearly comparable with controls (45.1±11.95 years) with no significant difference. However, the categorization of the study population into age groups revealed that the age group between (31-45) years was more frequent among patients than control group with a significant difference. Also, the mean age for females was (46.19±11.52 years) while the mean age for males was (44.16±10.69 years). Sex frequency was comparable between the two groups with no significant difference. RA patients had significantly higher body amss index (BMI) than control group (27.6±4.77 kg/m^2 versus. 25.31±4.0 kg/m2). The frequency of smokers among patients and control group was 35% and 19%, respectively, with a significant difference. Finally, none of controls had a family history of RA while 32% of patients had such a history, with a highly significant difference (Table 2).

Table 2. Demographic characteristics of the study population

Variables		Patients (n=100)	Controls (n=100)	P value
Age (years)	Mean±SD	46.22±11.33	45.1±11.95	0.059
	Range	20-75	18-75	
	16-30	9 (9%)	15 (15%)	0.039
	31-45	42 (42%)	31 (31%)	
	46-60	35 (35%)	48 (48%)	
	61-75	14 (14%)	6 (6%)	
	Female	46.19±11.52	41.91±11.52	0.296
	Male	44.16±10.69	46.06±11.88	0.095
Sex	Male	25 (25%)	31 (31%)	0.345
	Female	75 (75%)	69 (69%)	
Body mass index (kg/m^2)	Mean±SD	27.6±4.77	25.31±4.0	<0.001
	Range	17.3-45.55	16.37-37.0	
	Underweight	6 (6%)	4 (4%)	0.005
	Normal	24 (24%)	46 (46%)	
	Overweight	40 (40%)	35 (35%)	
	Obese	30 (30%)	15 (15%)	
Smoking	No	65 (65%)	81 (81%)	0.011
	Yes	35 (35%)	19 (19%)	
Family history	No	68 (68%)	100 (100%)	<0.001
	Yes	32 (32%)	0 (0%)	

Serum levels of TNF-α, TNFRII and IL-17 in studied groups

The median serum level of TNF-α was significantly higher in RA patients than control group (94.26 ng/l versus 59.7 ng/l). While the serum level of TNFRII was higher in control group than in patients' group with a significant difference (10.7 ng/ml versus 7.03 ng/ml). Moreover, the median serum level of IL-17 in patients (54.3 ng/l) was significantly higher than in the control group (40.35 ng/l) (P <0.001 for all) (Table 3).

Table 3. Serum Levels of TNF-α, TNFRII, and IL-17 in RA patients and control group

Marker		Patients (n=100)	Controls (n=100)	P value
TNF-α (ng/l)	Mean±SD	101.92±46.33	99.8±111.93	<0.001
	Median	94.26	59.7	
	Range	57.1-322.82	29.1-651.77	
TNFRII (ng/ml)	Mean±SD	15.09±13.66	15.09±13.66	<0.001
	Median	7.03	10.7	
	Range	4.19-22.34	4.11-79.04	
IL-17 (ng/l)	Mean±SD	68.16±40.96	44.08±19.23	<0.001
	Median	54.3	40.35	
	Range	36.35-207.48	21.28-120.2	

Diagnostic Values of TNF-α, TNFRII and IL-17

ROC curve was used to evaluate the diagnostic value of TNF-α, TNFRII and IL-17 in discrimination between patients with RA and control group. For TNF-α, the area under the curve (AUC) was 0.775, 95% CI = 0.697-0.853, P <0.001, the sensitivity and specificity of the test at cut-off value of 78.41 ng/l was 81% and 74%, respectively. For TNFRII, the AUC was 0.821, 95% CI = 0.756-0.885, P <0.001, the sensitivity and specificity of the test at cut-off value of 7.8 ng/ml was 80% and 77%, respectively. While for IL-17, the AUC was 0.793, 95% CI = 0.726-0.859, P <0.001. The sensitivity and specificity of the test at cut-off value of 46.91 ng/l was 80% and 71%, respectively (Table 4).

Table 4. Diagnostic value for TNF-α, TNFRII and IL-17 in discrimination between patients with RA and control group

Marker	AUC	95%CI	Sensitivity	Specificity	Cut off value	P value
TNF-α	0.775	0.697-0.853	81%	74%	78.4 ng/l	<0.001
TNFRII	0.821	0.756-0.885	80%	77%	7.8 ng/ml	<0.001
IL-17	0.793	0.726-0.859	80%	71%	46.91 ng/l	<0.001

Association of clinical factors with early clinical responsiveness

The mean number of infliximab doses and treatment duration was 4.76±1.23 doses and mean duration of treatment was 4.64±1.69 months for responder and 4.48±1.54 doses and 4.68±1.21 months for non-responder (Table 5).

Table 5. Association of Clinical Factors with early clinical responsiveness

Variables		Responders (n=50)	Non-responders (n=50)	P value
Number of doses of infliximab	Mean±SD Range	4.76±1.23 2.0-7.0	4.48±1.54 2.0-6.0	0.746
Duration of treatment (months)	Mean±SD Range	4.64±1.69 3.0-6.0	4.68±1.21 2.0-6.0	0.622

Serum Levels of TNF-α, TNFRII and IL-17 in responder and non- responder patients

The median serum level of TNF-α and IL-17 in non-responder patients were (98.52 ng/l and 59.16 ng/l respectively), which were higher than those of responder one (86.12 ng/l and 50.83 ng/L respectively) with a significant difference. Regardless of the higher median level for TNFRII in non-responder patients but there were no significant differences (Table 6).

Table 6. Serum Levels of TNF-α, TNFRII, and IL-17 in patients' groups

Marker		Responder (n=50)	Non-responder (n=50)	*p*-value
TNF-α (ng/l)	Mean±SD	90.78±24.89	115.83±61.33	0.001
	Median	86.12	98.52	
	Range	57.36-221.9	57.1-322.82	
TNFRII (ng/ml)	Mean±SD	7.06±1.88	8.37±4.19	0.175
	Median	6.84	7.22	
	Range	4.19-16.61	8.82-22.34	
IL-17 (ng/l)	Mean±SD	62.21±36.56	75.60±45.25	0.006
	Median	50.83	59.16	
	Range	36.35-207.84	37.69-205.39	

Correlation of TNF-α, TNFRII and IL-17 with other variables

TNFRII displayed a significant positive correlation with TNF-α (r = 0.161, P = 0.031). IL-17 had a significant negative correlation with final clinical disease activity index (CDAI) (r = -0.262, P = 0.012) while had a significant positive correlation with each of TNFRII (r= 0.249, P = 0.001), TNF-α (r = 0.339, P <0.001) as shown in (Table 7).

Table 4. Correlation of TNF-α, TNFRII, and IL-17 with other variables

Variables	TNF-α		TNFRII		IL-17	
	r	P value	r	P value	r	P value
Age	0.137	0.067	0.022	0.764	0.117	0.118
Weight	0.055	0.463	-0.150	0.044	0.005	0.951
Height	-0.004	0.959	0.063	0.401	0.046	0.543
BMI	0.081	0.282	-0.210	0.005	-0.015	0.841
Treatment Duration	0.058	0.585	0.083	0.438	-0.130	0.224
Final CDIA	-0.248	0.007	-0.176	0.096	-0.262	0.012
Dose	-0.004	0.972	0.085	0.426	-0.184	0.082
TNF-α			0.161	0.031	0.339	<0.001
TNFRII					0.249	0.001

Discussion

In the present study, the mean age in patients was 46.22±11.33 years and the rate of RA increased at the age groups (31-45 years), while Al-Hassan et al. showed that the mean age of the patient's group was 42.3 years [12]. It is noteworthy that the age range of 30-50 years is considered the working age in the Iraqi population, and this factor may play a significant role in the increased onset of certain diseases. Conversely, as individuals age, the probability of developing autoimmune diseases tends to rise due to enhanced tissue damage and apoptosis, consequently leading to a higher frequency of autoantibodies.

Current findings demonstrated a higher prevalence of RA in females (75%) compared to males (25%). Consistent with this result, Kvien et al. also reported a higher frequency of RA in females than in males [13]. This study also showed that the ratio of females to males

about 3:1. The reasons for this overrepresentation of women are not completely clear, but genetic (X-linked) factors and hormonal aspects are likely to be involved [(14)]. Cutolo, et al. found that the increase of estrogen level and the decrease of androgen level in the RA synovium fluids seem to play an important role in the immune/ inflammatory local response [(15)]. While Da Silva, et al. discussed that some studies have shown that sex hormones can interfere with many hypothesized processes in the pathogenesis of RA, including immune regulation, inflammatory mediators, interaction of cytokine system, and direct influence of cartilage [(16)]. It is hypothesized that women between the ages of 40 and 60 are more likely to develop RA compared to men, due to undergoing hormonal changes during menopause. Menopause decreases estrogen and progesterone levels, which is thought to serve as a protective mechanism for bones and joints. Estrogen in larger quantities can decrease inflammation by increasing regulatory cytokines such as IL-10 and transforming growth factor-β (TGFB), which is why it is believed to act as a protective mechanism against RA and Sjogren's syndrome [(17)].

Regarding BMI, the present study revealed a significant increase in the risk of RA among overweight and obese patients. These findings align with the research conducted by Lu et al., 2014 [(14)], which also reported a similar association between RA the risk and higher BMI. There was evidence suggesting a role of obesity in the development of other chronic diseases, such as type 2 diabetes and cardiovascular disease [(18)]. It is hypothesized that adipose tissue may be exerting its effects on the pathogenesis of these diseases via inflammatory adipokines, the systemic overload of adipose-derived cytokines is a proposed cause of immune, endocrine, reproductive and metabolic dysfunction in obesity, adipokines originate in adipose tissue and are secreted by adipocytes and adipose-resident macrophages, adipocytes present in obese and overweight individuals have been shown to secrete inflammatory markers such as C-reactive protein (CRP), amyloid A, TNF-α, IL-6, IL-1β, monocyte chemotactic protein-1 (MCP-1), and macrophage migration inhibitory factor (MIF) [(19,20)]. Studies have shown significantly elevated levels of these inflammatory markers in preclinical RA [(21-23)].

This work found that smoking significantly increases risk of RA. The mechanism by which smoking influences RA susceptibility/severity is unclear at present, although it may have direct effects on the disease process by inducing and/or increasing the production of RF or by producing alterations in the immune system [(24)]. Cigarette smoke condensate (CSC) induces pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6 and IL-8, at both mRNA and protein levels in RA-affected Fibroblast-like synoviocytes (FLS). Moreover, TNF-α is known to induce the expression of IL-1α, IL-1β, IL-6 and IL-8 mRNA, which are augmented by CSC. Among these proinflammatory cytokines, IL-1 and TNF-α are strongly associated with the pathogenesis in RA [(25)].

The current study provides evidence that having a positive family history significantly increases the risk of developing RA. These findings are in line with the research by Thomas et al.,2016 who also emphasized that family history is one of the most potent and well-established risk factors for the development of RA [(26)].

This study observed that the serum level of TNF-α was significantly higher among RA patients than control and this goes with other studies such as Ingegnoli et al. [(27)] in which even after 14 weeks of infliximab treatment, the levels of TNF-α remained higher in patients than control. Other previous study also found that TNF-α levels were significantly higher in RA patients compared to healthy controls [(28)]. The higher serum levels of TNF-α in RA patients compared to healthy controls are likely due to the dysregulation of the immune system that occurs in this disease, resulting in increased production and release of TNF-alpha by immune cells.

The current study's findings revealed that the serum levels of TNFRII were significantly higher in control compared to the patients group.

These results were opposite to a previous Iranian study conducted by Ebrahimi et al., [29]. Also, a study by Cope et al. found that the serum levels of sTNF-R2 were 3-4 times higher than the levels of sTNF-R1. Both sTNF-R2 and sTNF-R1 were significantly elevated in patients with RA when compared to healthy controls [30].

The research findings revealed that patients with RA had significantly higher levels of IL-17 compared to the control group. These results are consistent with a study conducted by Muhammed et al., which also found elevated levels of serum IL-17 and IL-15 in RA patients from an Iraqi sample, with a strong and highly significant correlation between these cytokines [31]. Moreover, another study by Liu et al. explored the role of IL-17 in anxiety and depression in 18 RA patients compared to 18 healthy individuals. The results demonstrated that serum IL-17 levels were significantly higher in RA patients than in the healthy controls [32]. Since there was an imbalance in the immune system in RA that leads to the overproduction of pro-inflammatory cytokines such as IL-17. This imbalance could be due to the activation of immune cells such as dendritic cells and macrophages, which produce factors that promote the development of T helper 17 (Th17) cells. So, targeting IL-17 and Th17 cells is a strategy for the treatment of RA.

The finding of this study that non-responder patients (based on disease activity score CDAI) had significantly higher TNF-α serum levels than responder patients. These results suggested that these patients did not respond well to the TNF-α inhibitors in terms of symptom improvement or disease management. The elevated TNF-α levels may indicate that the medication was not effectively blocking the action of TNF-α in these individuals, leading to continued inflammation in disease activity and this may be because of individual variability in which the response to TNF-α inhibitors can vary among individuals due to genetic factors or differences in the underlying disease mechanisms. Certain patients may exhibit a unique genetic profile or have specific disease characteristics that contribute to their reduced responsiveness to TNF-α inhibitors. Additionally, in some cases, the underlying pathogenesis of the disease may involve alternative inflammatory pathways. In these situations, relying solely on targeting TNF-α may not lead to a satisfactory treatment response. To achieve better outcomes in such patients, alternative treatment approaches that target different inflammatory pathways may be more effective. Regarding TNFRII, current results showed that TNFRII serum level was higher in non-responder patients compared to responder patients. When TNF-α binds to TNFRII, it triggers a series of signaling events that contribute to the inflammatory response. Higher levels of TNFRII in the serum may suggest that there was an increase in the expression or shedding of this receptor in non-responder patients. This could indicate a more pronounced TNF-α signaling or activation despite treatment with TNF-α inhibitors. However, in non-responder patients, elevated TNFRII levels may suggest that the TNF-α inhibitors are not effectively blocking TNF-α binding to its receptor. This persistent TNF-α signaling could contribute to ongoing inflammation and disease activity, leading to a lack of response to the treatment.

The current study reveals that non-responders had notably higher levels of IL-17 in their serum. This suggests that despite receiving TNF-α inhibitors, these individuals continued to produce or release higher amounts of IL-17. The increased IL-17 levels in non-responders might indicate the involvement of an alternative pathway in driving the pathogenesis of RA in these patients. persistent activation of the Th17 pathway contributes to ongoing inflammation and disease activity in this subgroup.

There was a positive correlation between TNFRII and TNF-α in RA, this implied that higher levels of TNFRII were associated with higher levels of TNF-α.

TNF-α could induce the expression of TNFRII in certain immune cells. This suggests a feedback mechanism in which TNF-α stimulates the production of TNFRII, potentially enhancing its own signaling. This positive feedback loop may

contribute to the sustained inflammatory response observed in RA. These correlations may indicate potential interactions and pathways involved in the inflammatory processes and autoimmune response observed in RA.

Moreover, present work revealed a positive correlation between IL-17 and each of TNF-α and TNFRII. IL-17 has been found to potentiate the effects of IL-1 and TNF-α on synoviocytes, resulting in a synergistic increase in cytokine production. This indicates that IL-17 plays a crucial role as an activator of T cell-driven inflammation, thereby contributing to the development of rheumatoid arthritis (RA) [33]. Furthermore, the combination of IL-17 and TNF-α has been shown to trigger the production of pro-inflammatory mediators, including IL-1β, IL-6, IL-8, prostaglandin E2, and MMPs, leading to the progression of early inflammation towards chronic arthritis [34]. When anti-TNF-α drugs are used to block TNF-α signaling, the immune system may compensate by upregulating other inflammatory mediators, including IL-17. The positive correlation observed between IL-17 and TNFRII suggests that as IL-17 levels increase, the expression of TNFRII also tends to rise. This could be a compensatory mechanism to sustain the inflammatory response in the absence of TNF-α signaling. Evaluating the serum levels of pro-inflammatory cytokines such as TNF-α and IL-17 is crucial in determining the appropriate targets for drug interventions. Understanding the interplay between these cytokines can provide valuable insights for developing more effective treatment strategies for managing RA and other inflammatory conditions.

In conclusions, elevated levels of TNF-α, TNFRII, and IL-17 were observed in RA patients compared to the control group. Furthermore, non-responder patients exhibited significantly higher levels of these serum markers compared to responders. ROC analysis revealed that TNF-α, TNFRII, and IL-17 have good diagnostic value in discriminating between RA patients and control group.

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Author contribution

Dr. Fadhil: Project design, performing, doing the tests of the research, interpretation of the results, writing and manuscript preparation; Dr. Abbas: Project design, reviewing the article, and interpretation of the results. Dr. Al-Osami: Facilitated patient recruitment and aided in the collection of samples.

Conflict of interest

The authors declare there is no conflict of interest.

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