ASSESSMENT OF THE ROLE OF IL-17A IN RHEUMATOID ARTHRITIS PATIENTS; IN SULAYMANIYAH GOVERNORATE

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling and tenderness, with destruction of synovial joints, leading to severe disability and premature mortality. The etiology and pathogenesis of RA remain unknown, it is generally considered an autoimmune pathology in which autoreactive T cells of pathogenic potential, such as Th1 and Th17 cells, are thought to play an important role. Th17 cells selectively produce the signature cytokines such as IL-17, IL-21 and IL-22, and have been demonstrated to play a critical role for the chronic inflammatory response and subsequent tissue damage in the affected joints.

Objectives: To assess the role of IL-17A in RA; by estimation of the serum IL-17A levels in RA and apparently healthy controls, and assessing the association of serum IL-17A levels with disease activity and severity measured by DAS-28 by ESR.

Patients and Methods: Cross-sectional analytic study carried out in the division of rheumatology/Shaheed Hemin general hospital, in Sulymaniyah city from (January 2015 to September 2015); on 45 RA patients; and 45 age and gender matched apparently healthy controls. Measurements of serum IL-17A were done for both patients and controls by ELISA according to the manufacturer's instructions. Disease activity was determined in the patients; according to DAS-28 by ESR.

Results: A significant association was observed between serum IL-17A level and RA ($p<0.001$). There was a significant difference in serum IL-17A levels among RA patients on non-biological therapy and controls ($p<0.001$), also there was a significant difference in serum IL-17A levels among RA patients on biological therapy and controls ($p<0.001$), and no significant difference

was observed between the serum levels of IL-17A of RA patients on biological therapy and those on non-biological therapy (p=0.4), There was a significant association between serum IL-17A level and active RA disease (p<0.001).

Conclusions: Serum IL-17A has a diagnostic value in RA, demonstrated by significant differences in serum IL-17A levels of RA patients and controls. Elevated serum IL-17A levels in RA patients parallel the degree of disease activity and severity. This may highlight the usefulness of IL-17A as a possible biomarker for more aggressive joint involvement and damage, giving it an important prognostic and predictive value.

Keywords: Rheumatoid Arthritis, DAS-28, IL-17A

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling and tenderness, with destruction of synovial joints, leading to severe disability and premature mortality. Given the presence of autoantibodies, such as rheumatoid factor (RF) and anti–citrullinated protein antibody (ACPA) (tested as anti–cyclic citrullinated peptide [anti-CCP]), which can precede the clinical manifestation of RA by many years (Aletaha D et al., 2010).The patient should fulfill the new 2010 ACR/EULAR classification Criteria to be classified as definite RA, which is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints (score range 0–5), serologic abnormality (score range 0–3), elevated acute-phase response (score range 0–1), and symptom duration (2 levels; range 0–1) (Aletaha D et al., 2010).

RA is considered an autoimmune disease marked by joint inflammation, T cell infiltration of the synovium, synovial hyperplasia, neo-angiogenesis, involvement of many catabolic cytokines, and progressive destruction of articular cartilage and bone (Lubberts E et al., 2005).

The etiology and pathogenesis of RA remain unknown, it is generally considered an autoimmune pathology in which autoreactive T cells of pathogenic potential, such as Th1 and Th17 cells, are thought to play an important role (Park H et al., 2005) (Afzali B 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; therefore, inhibiting the action of pro-inflammatory cytokines by using specific cytokine

inhibitors or anti-inflammatory cytokines is the basis for new therapies (McInnes IB and Schett G, 2007) (Richard OW et al., 2007).

Th17 cells selectively produce the signature cytokines such as IL-17, IL-21 and IL-22, and have been demonstrated to play a critical role for the chronic inflammatory response and subsequent tissue damage in RA affected joints (Hemdan NY et al., 2010). Moreover, IL-23 is a pro-inflammatory cytokine involved in differentiation and activation of Th17 cells to produce IL-17 which was found to play a critical role in other rheumatic diseases as inflammatory bowel disease (IBD) (Gheita TA et al., 2014[1]) and Behçet's disease (Gheita TA et al., 2014[2]).

IL-17A is the most studied family member of the IL-17 family consisting of six cytokines called IL-17A to IL-17F (Kolls JK and Linden A, 2004).

The function of IL-17B-E is still poorly described, but IL-17A and IL-17F have been reported to have quite overlapping functions in autoimmunity, which could be explained by their structural homology. IL-17A and IL-17F can be secreted as homodimer or heterodimer (IL-17A/F) and bind to the IL-17 receptor (IL-17R) complex that is widely expressed throughout the body (Wright JF et al., 2007).

In the early stages of RA pathogenesis, angiogenesis plays an important role. IL-17 potently contributes to this process, by stimulating fibroblast like synoviocytes (FLS) to produce vascular-endothelial growth factor (VEGF) (Ryu S et al., 2005). Concordantly, local over-expression of IL-17 increased the vascularity in mouse ankles; and in Matrigel plugs the cytokine promoted the growth of blood vessels (Pickens SR et al., 2010). Additionally, IL-17 induced the secretion of various inflammatory mediators like IL-6, IL-8, prostaglandin E2 (PGE2), and granulocyte colony stimulating factor (G-CSF) from synovial fibroblasts. Neutralizing IL-17 (using a monoclonal antibody) blocked this induction, indicating that the effect is specific to thisTh17 cytokine (Fossiez F et al., 1996). As with synovial fibroblasts, IL-17 increased secretion of a select group of cytokines (e.g. IL-1b, TNFα, and IL-6) by human macrophages upon stimulation with recombinant protein (Jovanovic DV et al., 1998). In addition to the increased expression of these (pro-inflammatory) cytokines, IL-17 increased production of various matrix degrading enzymes, namely matrix metalloproteinase (MMP)-1, -2, -9, and -13 in whole synovial tissue, synovial fibroblasts, and cartilage (Moran EM et al., 2009).

Interestingly, various additive and synergistic effects were observed between IL-17 and the main cytokine known to be important in RA pathogenesis; TNF-α. For instance, combining IL-17 with TNF-α increased IL-6 secretion in an additive way, compared to secretion induced solely by IL-17. Furthermore, the combination of IL-17 and TNF-α induced GM-CSF

secretion by synovial fibroblasts, while the two cytokines separately showed no effect on GM-CSF secretion (Fossiez F et al., 1996). In murine knee joints, overexpression of solely IL-17 or TNF-α resulted in joint inflammation and bone erosion. Interestingly, when overexpressing both cytokines simultaneously, strikingly enhanced levels of joint inflammation and destructive capacity were observed. Additionally, S100A8, IL-1b, and MMP mRNA was strongly upregulated when both cytokines were overexpressed (Koenders MI et al., 2012). Treating mice during established arthritis with the combination of a soluble IL-17 receptor and TNF binding protein significantly inhibited further joint inflammation and cartilage destruction, more potently than either of the two anti-cytokine treatments alone (Koenders MI et al., 2011).

Neutralization of inflammatory mediators to reduce the 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. Therefore, anti-IL-17 therapy is very interesting as an additional new anti-rheumatic strategy for RA (Sarah LG, 2004).

A recent study demonstrated that in RA patients not responding to treatment with the, overall very effective, biological targeting TNF-α, increased levels of both Th17 cells and cytokines were observed (Yue C et al., 2010). Since the group of anti-TNF non-responders accounts for 30% of the RA patients, it is important to

investigate other treatment options for those patients. As Th17 cells seem to be linked with anti-TNF non-responsiveness, those cells or its effector cytokines might be interesting new targets in RA therapy (Notley CA et al., 2008).

Patients and Methods: A cross-sectional analytic study carried out in the division of rheumatology/Shaheed Hemin general hospital, in Sulymaniyah city from (January 2015 to September 2015), 45 rheumatoid arthritis patients were selected and fulfilled the 2010American College of Rheumatology (ACR) / European League against Rheumatism (EULAR) classification criteria for rheumatoid arthritis (Aletaha D et al., 2010) (Table 1).

Table (1): 2010 ACR/EULAR Criteria for RA

2010 ACR/EULAR Diagnostic criteria for RA

Categories	Score
Patients who need to be investigated: (1) At least one joint involved with definite clinical synovitis (2) Patients presenting with synovitis not explained by any other disease	
Classification criteria for RA (add scores of categories A-D; definite RA = a score of ≥6/10)	
A) Joint involvement	
• 1 large joint	0
• 2–10 large joints	1
• 1–3 small joints (with or without large joint involvement)	2
• ≥4–10 small joints (with or without large joint involvement)	3
• >10 joints (with at least 1 small joint involved)	5
B) Serology (at least 1 test result is needed for classification)	
• Negative RF and negative ACPA	0
• Low positive RF or low positive ACPA	2
• High positive RF or high positive ACPA	3
C) Acute–phase reactant (at least 1 test result is needed for classification)	
• Normal CRP and normal ESR	0
• Abnormal CRP or abnormal ESR	1
D) Duration of symptoms	
• <6 weeks	0
• ≥6 weeks	1

All patients were receiving disease modifying anti-rheumatic drugs (DMARDs), 23 patients on biological DMARDs, and 22 patients on non-biological DMARDs. In addition, 45 apparently healthy controls (age and gender matched with the RA patients) were included in this study.

Informed consents were obtained from all subjects (patients and controls) and the study was approved by the local ethics committee.

Full history taking and clinical examination were performed to the RA patients. Disease activity was assessed by measuring the disease activity score for 28 joints (DAS-28) by ESR (Prevoo ML et al., 1995) (Table 2). The DAS28 considers 28 tender and swollen joint counts, general health; patient assessment of disease activity using the 100 mm visual analog scale with 0=best, 100=worst), plus levels of an acute phase reactant (ESR [mm/hour]).

Table (2): DAS-28 Disease Activity Score for 28 joints

DAS-28 Score	Interpretation
<2.6	Remission
2.6-3.2	Low Disease Activity
>3.2-5.1	Moderate Disease Activity
>5.1	High Disease Activity

Blood samples were withdrawn from all the patients and healthy controls. Patients were subjected to the following laboratory Investigations: complete blood count (Advia60 cell counter; Bayer), erythrocyte sedimentation rate (ESR) mm/1st hour (Westergren method), serum C-reactive protein (CRP), rheumatoid factor (RF), Measurement of IL-17A was done for both patients and healthy controls by ELISA according to the

manufacturer's instructions (RayBiotech Human IL-17A ELISA Kit; USA).

Statistical Analysis

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 17 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables conducted and appropriate statistical tests performed, t-test was used to compare between two means. One way ANOVA analysis was used to compare between more than two means. Pearson Correlation test was used to assess relationship between continuous variables. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs.

Results

A total of 45 RA patients were included in this study with mean age of (49±14.4) years, females were more than males; with female to male ratio as 2.7:1 (Table 3).

Table 3: Demographic Characteristics of RA Patients

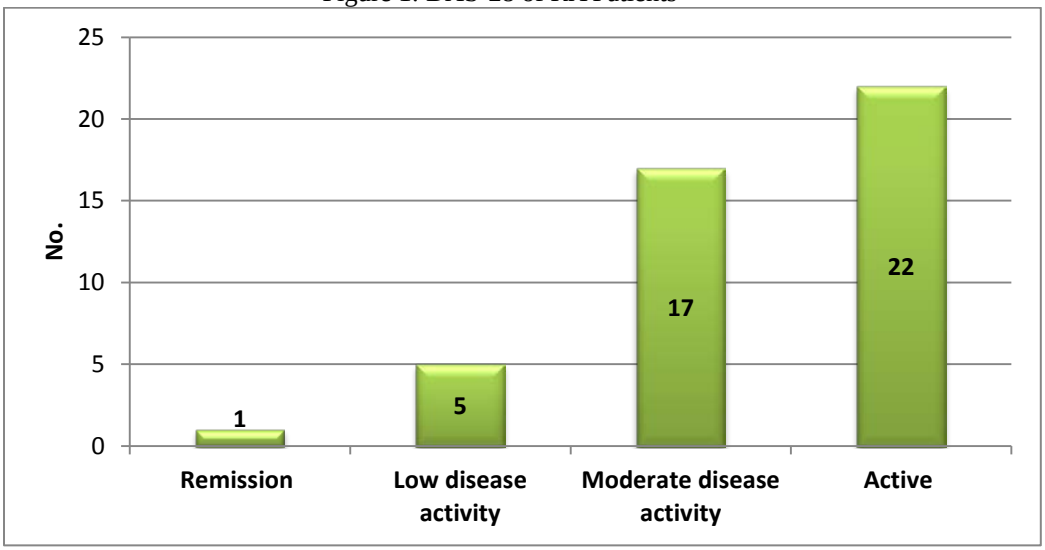
Variable	No.	%
Age Mean±SD (49±14.4) Years		
20-29 years	5	11.1
30-39 years	7	15.6
40-49 years	9	20.0
50-59 years	11	24.4
≥ 60 years	13	28.9
Total	45	100.0
Gender		
Male	12	26.7
Female	33	73.3
Total	45	100.0

Mean RA duration was 11.5±9.9 years, 62.2% of RA patients had RA duration as more than 5 years. Mean DAS-28 of RA patients was 5.03±1.4, 22 RA patients had active RA disease, 17 RA patients had moderate disease, 5 patients had low disease activity and only one patient had remission. (Table 4) (Figure 1).

Table 4: Duration and DAS-28 of RA Patients

Variable	No.	%
RA duration Mean±SD (11.5±9.9) Years		
<=5 years	17	37.8
> 5 years	28	62.2
Total	45	100.0
DAS-28 Mean±SD (5.03±1.4)		
Remission	1	2.2
Low disease activity	5	11.1
Moderate disease activity	17	37.8
High disease activity	22	48.9
Total	45	100.0

Figure 1: DAS-28 of RA Patients



Mean ESR of RA patients was 44.3±20.5 mm/hr, 84.4% of RA patients had high ESR. CRP was positive among 66.7% of RA patients (Table 5).

Table 5: ESR and CRP of RA Patients

Variable	No.	%
ESR Mean±SD (44.3±20.5 mm/hr)		
Normal	7	15.6
High	38	84.4
Total	45	100.0
CRP		
Positive	30	66.7
Negative	15	33.3
Total	45	100.0

More than half (51.1%) of RA patients were taking biologic therapy; and 48.9% of them were taking non-biologic therapy. Drugs taken by RA patients were distributed as the followings; Etanercept (35.6%), Methotrexate (35.6%), Rituximab (11.1%), HCQ (6.7%), Adalimumab (4.4%), SSZ (4.4%) and Leflonamide (2.2%). Most (91.1%) of RA patients had positive rheumatoid factor (RF) and 37.8% of them had positive family history (Table 6).

Table 6: Mode of Therapy, RF and Family History of RA Patients

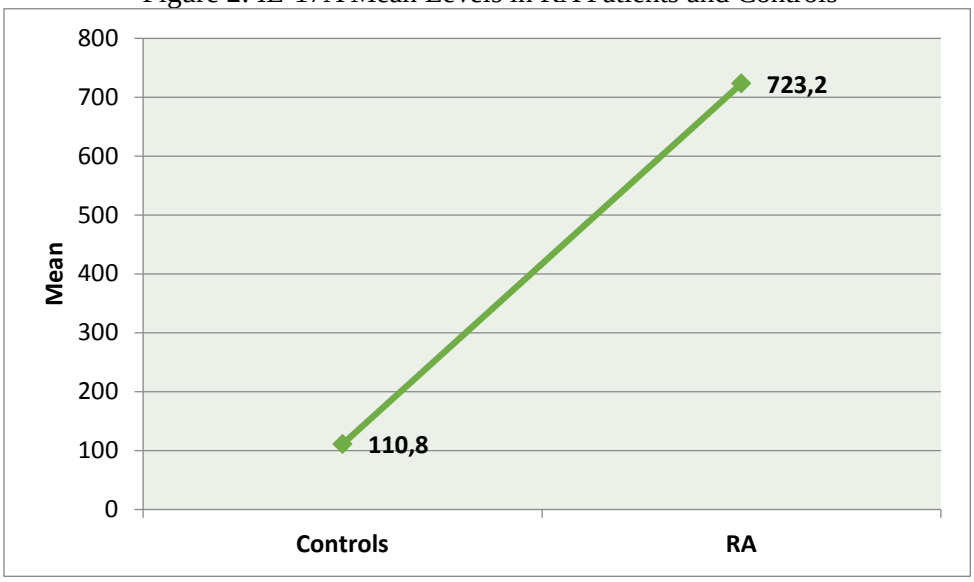
Variable	No.	%
Therapy		
Biologic therapy	23	51.1
Non-biologic therapy	22	48.9
Total	45	100.0
Drugs		
Etanercept	16	35.6
Adalimumab	2	4.4
Rituximab	5	11.1
Leflonamide	1	2.2
SSZ	2	4.4
Methotrexate	16	35.6
HCQ	3	6.7
Total	45	100.0
RF		
Positive	41	91.1
Negative	4	8.9
Total	45	100.0
Family history		
Positive	17	37.8
Negative	28	62.2
Total	45	100.0

There was a significant association between IL-17A level and RA, as there were significant differences in the serum levels of IL-17A of RA patients and controls ($p<0.001$) (Table 7) (Figure 2).

Table 7: IL-17A Mean Levels in RA Patients and Controls

Variable	RA	Controls	t-test	P
	Mean±SD	Mean±SD		
IL-17A	723.2±298.4	110.8±18	13.7	**<0.001**

Figure 2: IL-17A Mean Levels in RA Patients and Controls



There was a significant increase in IL-17A level in RA patients on non-biological therapy, compared to the controls ($p<0.001$).

There was a significant increase in IL-17A level in RA patients on biological therapy, compared to the controls ($p<0.001$).

No significant differences in IL-17A levels were observed between RA patients on biological therapy and those on non-biological therapy ($p=0.6$). (Table 8) (Table 9) (Figure 3)

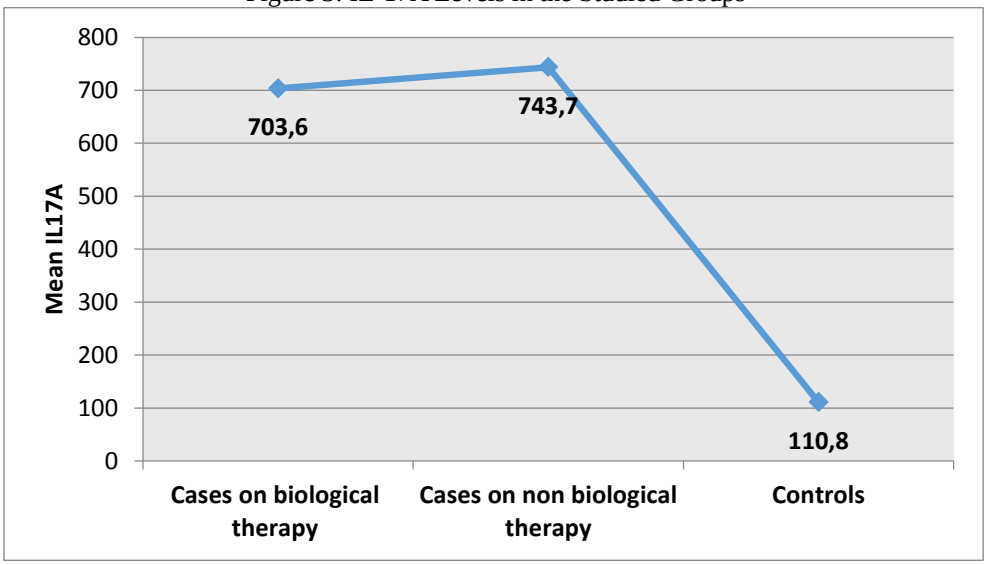
Table 8: IL-17A Levels in the Studied Groups

Categories	**IL-17A**
	Mean±SD
Cases on biological therapy	703.6±258.2
Cases on non-biological therapy	743.7±340.3
Controls	110.8±18
ANOVA (P value)	**<0.001**

Table 9: IL-17A According to RA Therapy

Variable	**Biological**	**Non-Biological**	**t-test**	**P**
	Mean±SD	**Mean±SD**		
IL17A	703.6±258.2	743.7±340.3	0.4	0.6

Figure 3: IL-17A Levels in the Studied Groups



There was a significant association between IL-17A level and active RA disease ($p<0.001$) (Table 10).

Table 10: Association between IL-17A and DAS-28 of RA Patients

DAS-28	**IL-17A**
	Mean±SD
Remission	295±0.0
Low disease activity	459.6±87.7
Moderate disease activity	638.4±152.3
High disease activity	868.2±338.1
ANOVA (P value)	**<0.001**

There was a significant association between IL-17A level and active RA disease in RA patients on biological therapy ($p=0.03$) (Table 11).

Table 11: Association between IL-17A and DAS-28 of RA Patients on Biological Therapy

DAS-28	**IL-17A**
	Mean±SD
Low disease activity	322±0.0
Moderate disease activity	576.3±132.7
High disease activity	803.7±267.3
ANOVA (P value)	**0.03**

A significant association was observed between IL-17A level and active RA disease among RA patients on non-biological therapy ($p=0.03$) (Table 12).

Table 12: Association between IL-17A and DAS-28 of RA Patients on non-Biological Therapy

DAS-28	**IL-17A**
	Mean±SD
Remission	295±0.0
Low disease activity	494 ±48.8
Moderate disease activity	693.6±153.9
High disease activity	981.1±432.8
ANOVA (P value)	**0.03**

Discussion

Over the past few years, the importance of IL-17 and T helper 17 (Th17) cells in the pathology of rheumatoid arthritis has become apparent. RA is a systemic autoimmune disease that affects up to 1% of the population worldwide. It is characterized by an inflamed, hyperplastic synovium with pannus formation, leading to bone and cartilage destruction in the joints. By the production of effector cytokines like IL-17 and IL-22, the T helper 17 subset protects the host against bacterial and fungal infections, but it can also promote the development of various autoimmune diseases like RA. Hence, the Th17 pathway recently became a very interesting target in RA treatment. Up to now, several therapies targeting the Th17 cells or its effector cytokines have been tested, or are currently under investigation (Roeleveld DM, Koenders MI, 2015).

The current study demonstrated a significant association between serum IL-17A level and RA, as there were significantly higher serum IL-17A levels in the RA patients compared to the healthy controls. The results of several investigators were in agreement with these results, like (Metawi et al., 2011) reported significantly higher serum IL-17A levels in 30 RA patients than 13 healthy controls, and (Melis L et al., 2010) demonstrated a high serum IL-17 level in 22 RA patients.

Furthermore, (Mika K et al., 2008) showed that the level of IL-17 gene expression in peripheral blood mononuclear cells (PBMC) from 52 RA patients was significantly higher than 34 controls (0.044±0.111 vs. 0.013±0.003, respectively, p=0.011). While in another study Serum IL-17 level was elevated in 41 RA patients compared to 21 healthy controls (Hitchon CA et al., 2004).

In addition, (Ziolkowska M et al., 2000) found a non-significantly higher serum IL-17 level in 15 RA patients compared to eight osteoarthritis (OA) patients (300 and 5 pg/mL, respectively).

To control the arthritis process by abrogation of inflammation, Disease Modifying Anti-Rheumatic Drugs (DMARDs) like methotrexate (MTX) and sulfasalazine are the first drugs to be administered to RA

patients. In the last decades, progress in the understanding of the cellular and molecular mechanisms of RA pathogenesis has led to the development of a new approach of treatment: the biologicals.

These biological agents can target a specific mediator of the disease, for example the pro-inflammatory cytokine TNF-α. Although the development and use of TNF-α inhibitors considerably improved prognosis of many RA patients, approximately 30% of patients still fail to respond adequately to this treatment. It was observed that in patients not responding to treatment with TNF-α inhibitors during RA therapy, circulating Th17 cell numbers were significantly higher compared to patients responding to treatment (Aerts NE et al., 2010) (Notley CA et al., 2008), suggesting that Th17 cells and Th17-derived cytokines might be interesting additional therapeutic targets in RA.

Very surprisingly, (Chen DY et al., 2011) reported that anti- TNF-α therapy causes a significant increase in Th17 cells in RA patients with an inadequate response to anti- TNF-α therapy. A high baseline level of IL-17 may have a predictive value for poor therapeutic response to TNF-α inhibitors. These interesting findings highlight the crucial role of IL-17A in the pathogenesis of RA and urge the need for biological therapies targeting IL-17A pathway.

There was a significant association between serum IL-17A level and active RA disease, which is comparable to the results of (Al-Saadany HM et al., 2015), as they demonstrated significant correlations between Th-17 cell percentages and serum levels of IL-17, with disease activity (DAS-28), ESR, CRP, TNF-α and MRI score of synovitis, and scores for disease severity and joint destruction.

In another study, (Metawi SA et al., 2011) revealed an increase in both serum and synovial IL-17A levels with higher DAS-28 scores and tender joint count (TJC), and increased serum IL-17A levels with higher swollen joint count (SJC). Similarly, (Melis L et al., 2010), reported elevated serum and synovial IL-17 levels in 22 RA patients that correlated significantly with local and systemic disease activity parameters.

Conclusion

Serum IL-17A has a diagnostic value in RA, demonstrated by significant differences in serum IL-17A levels of RA patients and controls.

Elevated serum IL-17A levels in RA patients parallel the degree of disease activity and severity. This may highlight the usefulness of IL-17A as a possible biomarker for more aggressive joint involvement and damage, giving it an important prognostic and predictive value.

Knowing that IL-17A is a key cytokine that is implicated in driving disease activity in RA makes it a very interesting potential therapeutic target

in RA treatment. Several therapies targeting IL-17A pathway have been tested, or are currently under investigation, with promising results as future novel biologic therapies in RA.

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