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Original Article

Rheumatoid Arthritis and Proinflammatory Cytokine IL-17

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Abstract

Introduction: Rheumatoid arthritis (RA) is the most common inflammatory joint disease. Various proinflammatory cytokines are involved in the pathogenesis of this chronic disorder. It is characterized by the presence of autoantibodies, such as rheumatoid factor and antibodies against citrullinated peptides. The present study focuses on investigation of possible association between the proinflammatory cytokine interleukin 17 and anti-CCP, anti-MCV, and anti-CarP antibodies seropositivity in RA patients.

Aim: To assess serum levels of interleukin 17 (IL-17) in patients with rheumatoid arthritis and healthy controls (HC) and to investigate the relationship between IL-17 and anti-cyclic citrullinated protein (anti-CCP) antibodies, anti-mutated citrullinated vimentin (anti-MCV) antibodies, and anti-carbamylated protein (anti-CarP) antibodies in patients with RA.

Materials and methods: Forty-seven patients diagnosed with rheumatoid arthritis and 44 healthy controls were included in the study. Serum IL-17 levels were examined in all participants. Anti-CCP, anti-MCV, and anti-CarP antibodies were tested in the group of RA patients.

Results: The mean serum level of IL-17 in RA patients was higher (12.8 pg/ml) than that in healthy controls (7.9 pg/ml), but the difference was not statistically significant (p=0.276). No significant correlation was observed between anti-CCP (+/−) and IL-17 (r_s=0.162, p=0.380), and between anti-MCV (+/−) and IL-17 (r_s=0.157, p=0.340). A significant positive correlation of moderate value was reported between anti-CarP (+/−) and IL-17 (r_s=0.388, p=0.015).

Conclusions: The present study demonstrated that the IL-17 serum levels in RA patients were increased compared to healthy controls. No correlation was found between ACPA immunological markers and IL-17 levels in patients with RA. A positive correlation was found between anti-CarP antibodies and IL-17 in the patients' group. The increased level of IL-17 is suggestive of its possible role in the pathogenesis of CarP positive RA patients.

Keywords

anti-CCP, anti-MCV, anti-CarP, IL-17, rheumatoid arthritis

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PENSOFT.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory joint disease with a main clinical manifestation of symmetrical progressive erosive polyarthritis, leading to cartilage and bone breakdown, and progressive, irreversible joint destruction.[1-3]

RA is the most common autoimmune inflammatory joint disease.[4,5] It affects all races and age groups, with the prevalence of the disease being estimated to be approximately 0.5%–1% of the population in Europe and North America.[1,2,6-8]

The etiology of rheumatoid arthritis is still unknown, but the polygenic autoimmune disease theory, with pathogenesis incorporating both genetic and environmental variables, including infectious agents, is quite relevant.[9,10]

Presence of autoantibodies is one of the main characteristics of RA.[11] Many of these disease-associated antibodies target products of post-translational modifications of proteins, such as citrullination, carbamylation, acetylation, and glycosylation.[11-15] Thus, each patient with RA is characterized by a spectrum of antibodies against post-translationally modified proteins.[16]

Anticitrullinated peptide antibodies (ACPA) target a wide range of citrullinated antigens, such as fibrinogen, vimentin, α-enolase, filagrin, collagen type II, biglican, keratin and histones, and their polyreactivity against citrullinated residues has been demonstrated.[11,17-19] These include antibodies against cyclic citrullinated proteins – anti-CCP antibodies, antibodies against mutated / recombinant / modified citrullinated vimentin – anti-MCV, anti-CarP antibodies – against citrullinated vimentin, antibodies directed against citrullinated areas of fibrinogen, α-enolase, collagen type I and II, etc.[1] In addition to rheumatoid factor, the 2010 ACR / EULAR classification criteria for RA include the ACPA antibodies.[3,20-22]

Carbamylation of proteins leads to loss of their standard structure and impaired tolerance and ultimately to the formation of autoantibodies against carbamylated proteins – anti-CarP antibodies.[15]

Cytokines involved in the pathogenesis of RA

Several inflammatory mediators, including cytokines, cause mononuclear cell infiltration into the synovium and cartilage and bone destruction. These cytokines affect the interaction between cellular, immunological and biochemical mediators of inflammation at many levels.[23] Proinflammatory cytokines such as TNF-α, IL-1β, IL-17, and IFN-γ play a critical role in the pathogenesis of RA.[24]

The involvement of TNF-α and IL-1, which are interrelated in regulatory processes through a positive feedback, is crucial as they cause most of the pathological changes. These cytokines are the major inducers of fibroblast proliferation in pannus that produce collagenase and other proteolytic enzymes, which in turn cause cartilage destruction. They also activate osteoclasts for bone demineralization and stimulate angiogenesis, which cause systemic symptoms such as malaise, fatigue, and increased acute phase reactants in serum. The IL-23/IL-17 axis has been shown to play an essential role in the pathogenesis of autoimmune processes, such as experimental autoimmune encephalomyelitis, type 1 diabetes mellitus, and uveitis. In RA, IL-17 is detected in the synovium, and this cytokine has been shown to synergize with IL-1 to induce production of IL-6 by synovial fibroblasts and enhance the expression of specific chemokines in connective tissue. IL-17 is produced by Th17 and other cells[23,25]; it stimulates the secretion of TNF-α, IL-1β, and chemokines by macrophages and other cell types. Transforming growth factor-β (TGF-β) and IL-6 induce the differentiation of Th17 cells, while IL-23 secreted by the antigen-presenting cells (APCs) facilitates the expansion and maintenance of this subset of T cells.[23]

IL-17 induces many chemokines and cytokines, in part by activating NF-κB via the classical pathway and exhibits pronounced synergism with TNF-α. Th1 cells are primarily responsible for cell-mediated immunity and Th2 cells for humoral immunity. An additional helper T-cell type called Th17 has been identified after labeling its cytokine IL-17, suggesting the involvement of Th17 and IL-17 in the pathogenesis of RA. The effect of IL-17 is significantly enhanced by synergism with TNF-α, which is produced by T cells and activated macrophages. Activated macrophages also produce IL-6 and IL-1. Interleukin 6, in some cases IL-1, TNF-α, and IL-17, in addition to TLR-2 and -4 ligands, directly or indirectly leads to the expression of RANK ligand (RANKL) on osteoblast stromal cells and synoviocytes, and RANKL is the central mediator of osteoclastogenesis that is essential for the function of mature osteoclasts. Th17 cells can directly stimulate this process, as only this T-helper class preferentially expresses RANKL. In addition, IL-17 regulates osteoprotegerin, the natural antagonist of RANKL. The increased ratio of RANKL to osteoprotegerin ensures the generation of osteoclasts from monocyte precursors and the continued activation and maintenance of mature osteoclasts that erode bone and thus participate in pathological processes in RA IL-1 and TNF-α, also directly contributing to a differential of osteoclasts and their activation. Neutrophils activated by IL-17-induced chemokines also further contribute to tissue destruction. Proinflammatory cytokines, including TNF-α, IL-1, and IL-17, induce the classical NF-κB activation pathway. Th17 cells produce IL-17A (also known as IL-17), as well as IL-17F, which is thought to have the same biological activity as IL-17, although it has a lower affinity for the IL-17 receptor.[25] Interleukin 17 has been implicated in the pathogenesis of numerous autoimmune diseases including RA.

AIM

The aim of the study was to evaluate and compare the serum IL-17 levels of RA patients and healthy controls and

to investigate the relationship between serum levels of the inflammatory mediator Il-17 and anti-CCP, anti-MCV, and anti-CarP antibodies in patients with RA.

Patients

Ninety-one participants were included in the study. The patient group consisted of 47 patients diagnosed with RA (22% men and 78% women) with a mean age of 59±12, hospitalized in the Clinic of Rheumatology of Kaspela University Hospital and the Rheumatology Department of COH Hospital. The control group included 44 healthy subjects (32% men and 68% women) with a mean age of 49±13 years.

Patients with RA were diagnosed according to the Classification Criteria of ACR/EULAR 2010. The average duration of the disease was 8 years. Disease activity was assessed according to the accepted DAS 28 disease activity scoring system. According to this scale, patients were assessed with high disease activity (DAS 28>5.1), moderate disease activity (5.1<DAS 28>3.2), low disease activity (3.2<DAS 28>2.6), and remission (DAS 28<2.6).

The inclusion criteria for the patient group were the following: adult patients (18 – all -19-82, RA 31-82, HC 19-79 years); diagnosed RA according to ACR/EULAR 2010 criteria; a stable dose of DMARDs for a period of three months prior to enrollment; lack of other rheumatic disease. The inclusion criteria for the control group were age ≥18 years old, and no evidence of rheumatic disease.

All patients were on stable drug modifying anti-rheumatic drugs (DMARDs) therapy for at least three months at the time of blood sampling. All the patients received DMARDs – conventional synthetic DMARDs (csDMARDs) (methotrexate, leflunomide) (n=47), biologic agents (bDMARDs) (n=3), and combination of csDMARDs with bDMARDs (n=14).

The study was conducted according to the requirements of Good Clinical Practice and in compliance with the Declaration of Helsinki. All participants signed informed consent prior to enrollment in the study. The study was approved by the Local Ethics Commission.

MATERIALS AND METHODS

Laboratory studies

The immunological tests were performed in the Department of Medical Biochemistry, Faculty of Pharmacy, in the Medical University of Plovdiv. Anti-MCV antibody – an ELISA Kit from ORGENTEC Diagnostika, Mainz – Germany was used to test IgG class autoantibodies against mutated citrullinated vimentin (MCV). Anti-CCP antibody – anti-CCPhs (high-sensitive) from ORGENTEC Diagnostika, Mainz – Germany were used to test autoantibodies against cyclic citrullinated peptides (CCP) IgG class. Human IL-17A A – human IL-17A ELISA kit, Diaclone, France, was used to test human IL-17A. Anti-CarP antibodies – human anti-carbamylated protein antibody (ACPAb) ELISA Kit from Sincere Biotech, China was used to test anti-carbamylated antibodies.

Statistical analysis

Data analysis was performed using IBM SPSS, version 24 (2016). The serum levels of IL-17 in the RA patients and healthy controls were compared using the Mann-Whitney U test. Associations between serum levels of IL-17 with anti-CCP, anti-MCV, and anti-CarP were established using Spearman rank-order correlation. Receiver operating characteristic (ROC) curve was used to examine the ability of IL-17 to distinguish between anti-CarP (+/−) cases. The results were interpreted as statistically significant at $p<0.05$.

RESULTS

Comparison of IL-17 levels in RA patients and healthy controls

IL-17 levels were assessed in 47 RA patients and 44 healthy controls **(Table 1)**. In patients with RA, the median serum level of IL-17 was higher (7.0 pg/m) than in healthy controls (3.9 pg/m) with no statistically significant difference ($p=0.11$).

Relationship between IL-17 levels and anti-CCP, anti-MCV, and anti-CarP antibodies in RA patients

Spearman rho correlation analysis was used for this analysis because association was sought between data encoded on a dichotomous scale (0-1) – anti-CCP, anti-MCV, and anti-CarP and others measured by continuous scale – (IL-17).

The correlation coefficients are interpreted in relation to Cohen reference values (Cohen, 1988) as follows:

- very high / high correlation: ± (0.70 – 1)

Table 1. IL-17 levels in patients with RA and healthy controls

Group	N	Mean	SD	Median	IQR	Mann-Whitney (U)	*p*
RA	47	12.8	28.6	7.0	9.1	678.5	0.11
Healthy controls	44	7.9	7.03	3.9	5.1		

IRQ: interquartile range

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- large / high correlation: ± (0.50 – 0.69)
- medium / moderate correlation: ± (0.30 – 0.49)
- weak / low correlation: ± (0.10 – 0.29)
- Positive values indicate a positive linear correlation, while negative values indicate a negative linear correlation.

The correlation coefficients are presented in **Table 2**. No significant correlation was observed between anti-CCP (+/–) and IL-17 (r_s=0.162, p=0.380). There was no significant correlation between anti-MCV (+/–) and IL-17 (r_s=0.157, p=0.340). A significant positive correlation of moderate value was found between anti-CarP (+/–) and IL-17 (r_s=0.388, p=0.015).

The association between anti-CarP and IL-17 serum levels is illustrated by the ROC curve **(Fig. 1)**, showing a significant ability of IL-17 to distinguish anti-CarP positive from negative cases, AUC = 0.748 (95% CI 0.56–0.88, p=0.005). The optimal criterion IL-17 level was established as >3.61 pg/ml, with sensitivity of 72% and specificity of 80%.

Table 2. Spearman test results for the relationship between IL-17 levels and anti-CCP, anti-MCV, and anti-CarP antibodies in the sample of RA patients

Parameters	Statistics	IL-17
anti-CCP (+/–)	Spearman correlation coefficient	0.162
	p-value	0.380
	N	47
anti-MCV (+/–)	Spearman correlation coefficient	0.157
	p-value	0.340
	N	47
anti-CarP (+/–)	Spearman correlation coefficient	0.388
	p-value	0.0015*
	N	47

* significant at p<0.05

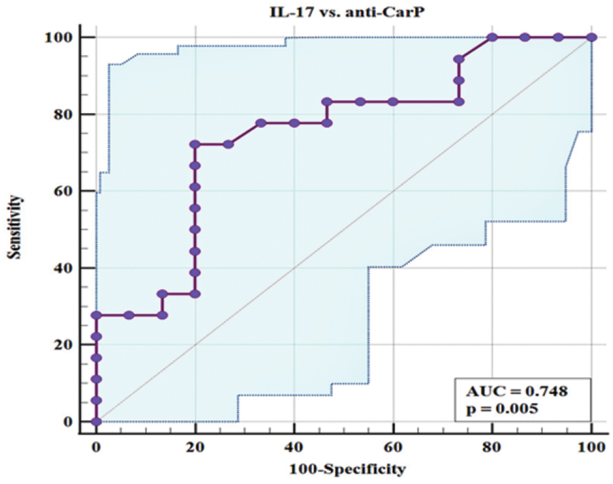

Figure 1. Rock curve illustrating the relationship between anti-CarP +/– and IL-17 levels in patients with RA.

DISCUSSION

Rheumatoid arthritis is a chronic inflammatory disease characterized by imbalance between pro- and anti-inflammatory cytokines.[26] In addition to TNF-α, IL-1β, and IL-6, other cytokines such as IL-23, IL-17, and interferon gamma (IFN-γ) play crucial roles in the pathogenesis of RA. Wu et al.[27] found experimentally that IL-17 and IL-22 could induce RANKL expression in human synovial fibroblasts, leading to a loss of RANKL/osteoprotegerin balance. This process causes enhanced osteoclastogenesis and bone erosion in autoimmune arthritis. IL-17 may increase the production of vascular endothelial growth factors in rheumatoid fibroblasts such as synoviocytes, contributing to angiogenesis in the rheumatoid synovium. In addition, IL-17 can stimulate the expression of various proinflammatory cytokines, e.g., IL-1β, TNF-α, IL-6 and enzymes that degrade the matrix – for example, matrix metalloproteinases in all synovial tissue, synovial fibroblasts, and cartilage, thus potentiating the inflammation and destruction of cartilage during the development of RA.[25] Scher et al. demonstrated a defect in the function of circulating Treg cells, elevated levels of Th17 cells, and their cytokine IL-17 in both plasma and synovium in RA patients.[28]

A recent meta-analysis reported that IL-17 levels were significantly higher in RA patients than in the control groups and that expression of IL-17A rs2275913, IL-17F rs763780 and IL-17A rs3819024 polymorphisms were significantly more expressed in RA patients.[29]

The role of IL-17 is well established in the pathogenesis of rheumatoid arthritis, as well as in other autoimmune and inflammatory diseases.[30,32] A number of researchers have studied the relationship between serum levels of cytokines and various proteins involved in the pathogenesis of RA. Qu et al. investigated serum level of IL-17 in RA patients and the correlation between IL-17 and 14-3-3g protein.[31] Medhat et al. found significantly increased mean serum IL-17 level in RA patients compared with controls.[32] This finding is consistent with some previous studies.[33-38] In addition, the authors assessed serum and synovial fluid (SF) level of IL-17 in RA patients and its correlation with disease activity and severity. Positive correlations of serum and SF IL-17 levels with power Doppler ultrasound (PDUS) findings and Larsen score were reported.

Despite the fact that anti-CCP and anti-MCV have been established in rheumatoid arthritis, there is growing evidence that these antibodies may be negative in some patients with certain rheumatoid arthritis. Our study provides another opportunity to improve the diagnostic process in patients with RA by examining a new autoantibody.

A number of investigators have found that IL-17 is a key cytokine in the pathogenesis of RA. However, many clinical trials investigating the efficacy of monoclonal antibodies targeting IL-17 have shown that blocking this pathogenetic axis is not predominant in RA. Knowledge of the pathways that control and suppress inflammation in RA are essential

and crucial for understanding the pathophysiology of the disease and developing new therapeutic strategies in RA.[39]

The present study focuses on the investigation of serum IL-17 levels in RA and healthy controls. In addition, we assessed association between serum IL-17 levels and seropositivity in RA group. The patients were tested for anti-CCP, anti-MCV, and anti-CarP antibodies. We found higher serum level of IL-17 in the patient's group than in the healthy controls, but the difference was not statistically significant. This finding is consistent with most of the data available in the literature. We found no significant correlation between ACPA (anti-CCP and anti-MCV) positivity and IL-17. The mean values of IL-17 in anti-CCP and anti-MCV positive and negative patients were similar. A moderate positive correlation was found between anti-CarP antibodies and IL-17. The mean values of IL-17 showed a significant difference in anti-CarP positive and negative patients. Carbamylation is dependent on myeloperoxidase and correlates with the inflammatory process. In this regard, an additional study in a larger group of participants of laboratory inflammatory activity compared with the two quantities would provide additional information. Ridgley et al. reviewed the predominant cytokines in early rheumatoid arthritis and considered their implications for future treatment strategies.[40] New roles for cytokines of the IL-23/Th17 axis, type I interferons, and IL-8 have been suggested in the progression of ACPA-positive arthralgia.[40]

CONCLUSIONS

The present study found increased serum level of IL-17 in RA patients compared to healthy controls although these differences were not statistically significant. The positive correlation between anti-CarP-antibodies and IL-17 serum level is highly suggestive of a possible role of this cytokine in the pathogenesis of RA in CarP positive patients.

Limitations

A limitation of the present study is its cross-sectional design. This could affect the obtained results. Another limitation is the lack of correlation with disease activity and radiographic stage of the disease.

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Conflict of Interest

The authors declare no conflicts of interest.

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Ревматоидный артрит и провоспалительный цитокин IL-17

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Резюме

Введение: Ревматоидный артрит (РА) является наиболее распространённым воспалительным заболеванием суставов. В патогенезе этого хронического заболевания участвуют различные провоспалительные цитокины. Он характеризуется наличием аутоантител, таких как ревматоидный фактор и антитела к циклическому цитруллиновому пептиду. Настоящее исследование сосредоточено на изучении возможной связи между провоспалительным цитокином интерлейкином 17 и серопозитивностью к анти-CCP, анти-MCV и анти-CarP у пациентов с РА.

Цель: Оценить сывороточные уровни интерлейкина 17 (IL-17) у пациентов с ревматоидным артритом и здоровых людей (КГ), а также изучить взаимосвязь между IL-17 и антителами к циклическому цитруллинированному пептиду (анти-CCP), антимутантными антителами. антитела к цитруллиновому виментину (анти-MCV) и антитела к карбамилированному белку (анти-CarP) у пациентов с РА.

Материалы и методы: В исследование были включены 47 пациентов с диагнозом ревматоидный артрит и 44 здоровых человека. Уровни IL-17 в сыворотке были исследованы у всех участников. Анти-CCP, анти-MCV и анти-CarP были протестированы в группе больных РА.

Заключение: Настоящее исследование показало, что уровни IL-17 в сыворотке у пациентов с РА были повышены по сравнению со здоровыми людьми из контрольной группы. Корреляции между иммунологическими маркерами АСРА и уровнями IL-17 у больных РА выявлено не было. Выявлена положительная корреляция между анти-CarP-антителами и IL-17 в группе больных. Повышенный уровень IL-17 позволяет предположить его возможную роль в патогенезе CarP-позитивных пациентов с РА.

Ключевые слова

анти-CCP, анти-MCV, анти-CarP, IL-17, ревматоидный артрит