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Role of interleukin-23 as a biomarker in rheumatoid arthritis patients and its correlation with disease activity

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ABSTRACT

Background: IL-23 is a pro-inflammatory cytokine belonging to the IL-12 cytokine family. IL-23 is essential for the differentiation of Th17 lymphocytes, a subtype of T lymphocyte implicated in chronic inflammatory/autoimmune mediated diseases. Experimental models of arthritis and clinical indications have highlighted an important role for Th17 lymphocytes in the pathogenesis of RA. However the role and mechanism of action of IL-23 in the pathogenesis of RA are still not fully understood.
Objective: This study was conducted to assess the level of IL-23 in patients with RA as well as the relationship between the IL-23 level and disease activity.
Methods: The study includes 77 patients with RA fulfilling the American College of Rheumatology (ACR) revised criteria for diagnosis of RA as well as 25 age and sex matched healthy subjects as controls. Patients were divided according to disease activity into four groups: DAS 28 score (< 2.6), 10 patients in remission, DAS 28 score between 2.6–3.2, 10 patients with low disease activity, DAS 28 score ranges between (3.2–5.1), 30 patients with moderate disease activity and DAS 28 score (< 5.1), 27 patients with High disease activity. Disease activity were determined by the 28-joint disease activity score (DAS 28). Anti-citrullinated protein antibodies (ACPA) was done. The levels of IL-23 were determined by enzyme-linked immunosorbent assay (ELISA).
Results: Serum level of IL-23 was significantly elevated in RA patients (78.92 ± 52.47) compared to control group (33.34 ± 3.99) ($P < 0.001$). However, no correlations were found between IL-23 and DAS 28 score, and other patients characteristics.
Conclusion: Our results imply that IL-23 may potentially play a role in the pathogenesis of RA and may be a useful biomarker for the diagnosis of this disease. Targeting the IL-23 cytokine may provide a new therapeutic approach in the treatment of RA.

Contents

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease predominantly manifest as polyarthritis with extra-articular complications. Articular affection in RA is characterized by progressively destructive joint inflammation, destruction of articular cartilage with bone and synovial hyperplasia. Various cell types are involved in the pathogenesis of RA, including T cells, antigen presenting cells, and endothelial cells [1]. Cytokines also play a fundamental role in the processes that cause inflammation, articular destruction and extra-articular manifestation associated with RA. IL-23 is a pro-inflammatory cytokine belonging to

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the IL-12 cytokine family, secreted by activated dendritic cells (DCs) and macrophages. IL-23 binds to an IL-23 receptor expressed on dendritic cells, macrophages and monocytes [2]. IL-23 is essential for the differentiation of T helper 17 (Th17) lymphocytes from naive $CD4^+$ T cells [3]. Th17 cells have been associated with the induction of autoimmune tissue inflammation and under the influence of IL-23 produce IL-17 and some other additional novel factors [4]. Recent reports have suggested that interleukin-17 (IL-17)-producing Th17 cells are a new subset of cells critical to the pathogenesis of RA. IL-17 induces the production of inflammatory cytokines such as IL-1, IL-6, IL-8, and tumor necrosis factor-α (TNF-α), and it has been detected in the serum, synovial fluid (SF), and synovium of patients with RA [5]. Th17 lymphocytes, when stimulated by IL-23 it promotes osteoclastogenesis inducing receptor activator for Nuclear Factor-k B Ligand (RANKL) on mesenchymal cells and in cultures of osteoblasts. RANKL involved in the regulation of osteoclastogenesis is a key factor of the bone erosion process, and stimulates endothelial cells, epithelial cells, and synovial fibroblasts to produce prostaglandin E2, IL-6, and IL-8 [6]. Van Bezooijen RL and his colleagues (2002) [7] and Lubberts E and colleagues (2005) [8] founded that in patients with RA, IL-17 is involved in the destruction of the extracellular matrix and juxta articular bone resorption, through the induction of synthesis of RANKL and matrix metalloproteases. Also Stamp LK et al 2009 [9] demonstrated that IL-23 gene expression is higher in $IL\text{-}17A^+$ versus $IL\text{-}17A^-$ membranes. In keeping with this, $IL\text{-}17A^+$ and $IL\text{-}23^+$ cells co-localize in synovial membranes. So in RA, IL-23 is an important determinant of the production of IL-17A, a cytokine of consequence in inflammation and bone destruction [10].

2. The aim of the work

This study was designed to assess IL-23 level and its role in the pathogenesis of RA and to examine the relationship between IL-23 and markers of activity in those patients, helping to identify novel diagnostic and/or therapeutic targets for arthritis in patients with RA.

3. Patients and methods

This study was conducted in AL-Zahra hospital of Al-Azhar University, Cairo, Egypt. The study consists of 77 patients with RA (patients fulfilling the American College of Rheumatology (ACR) revised criteria for diagnosis of RA [11] as well as 25 age and sex matched healthy volunteers served as control. Patients were selected from the department of internal medicine. They were eligible for the study if they were 20 years of age or older. All patients included in the study underwent a standard procedure consisting of detailed medical history as well as physical examination including the musculoskeletal system and Body mass index (BMI) was calculated (Table 1) and (Table 2). Patients with other autoimmune inflammatory disorders that affect the IL-23 level, such as ankylosing spondylitis, psoriasis, multiple sclerosis, sarcoidosis and inflammatory bowel diseases were excluded from the study. Disease activity was assessed using the 28-joint disease activity score (DAS28) [12]. RA patients were classified according to disease activity by using the DAS 28 score to the following groups:

I. DAS 28 score (<2.6), 10 patients in remission,
II. DAS 28 score between (2.6–3.2), 10 patients with low disease activity,
III. DAS 28 score ranges between (3.2–5.1), 30 patients with moderate disease activity,
IV. DAS 28 score (<5.1), 27 patients with High disease activity. Those who voluntarily decided to participate in the study were signed an informed consent.

Table 1
Biological data of the studied patients with rheumatoid arthritis and healthy controls.

	Age	BMI	RF %	CRP %	ESR mm/h
Control (25)	44.6 ± 10	30.9 ± 3.8	0	0	22 ± 1.75
Patients (77)	(46.5 ± 10.5)	31 ± 4.1	77 (100)	27 (77.1)	68 ± 30.5

RF: rheumatoid factor; CRP: C-reactive protein.
Data expressed as mean ± SD or median & range.

Table 2
Demographic data of RA patient groups.

Groups	I	II	III	IV
Age (years)	43.6 ± 8.6	44.6 ± 6.2	41.8 ± 12.1	46.7 ± 10.3
BMI	31.5 ± 5.2	31 ± 5	31.5 ± 4	31.1 ± 2.4
Duration (years)	5 (2 to −12)	9 (3 to −17)	8 (1 to −20)	11 (1 to −20)
NSJE	2 (0 to −7)	3 (0 to −4)	4 (0 to −6)	6 (2 to −12)
NBJE	4 (2 to −8)	4 (1 to −8)	5 (2 to −8)	4 (2 to −8)

NSJE: Number of small joints affected.
NBJE: Number of big joints affected.Data expressed as mean ± SD or median & range.

3.1. Laboratory studies

Blood samples were collected from all patients and control subjects. C-reactive protein (CRP) was performed by latex agglutination method purchased from Omega Diagnostics, Scotland, UK) [13], Rheumatoid factor (RF) test was performed by latex agglutination method purchased from Omega Diagnostics, Scotland, and UK [14], Anti-citrullinated protein antibodies (ACPA) was assayed by ELISA Kits manufacturer by Orgentec Diagnostika GmbH and IL-23 was assayed by ELISA Kit manufacturer by R&D Systems, Minneapolis, MN, USA.

3.2. Statistical method

IBM SPSS statistics (V. 21.0, IBM Corp., USA, 2012) was used for data analysis. Data were expressed as Mean ± SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage of categorizing data. The following tests were done:

(1) Comparison between two independent mean groups of parametric data using the Student t test. (2) Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test. (3) Ranked Spearman correlation test to study the possible association between each two variables among each group for non-parametric data. (4) Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards

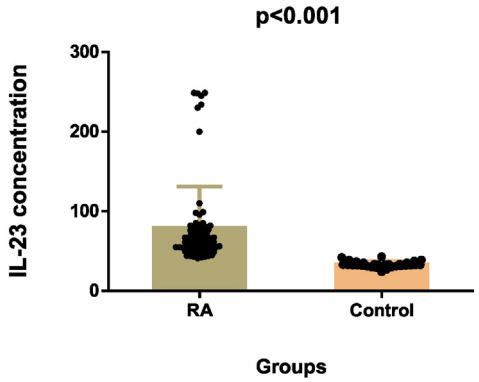

Fig. 1. IL-23 level in RA patients and healthy controls.