The Egyptian Rheumatologist (2014) 36, 21–27

Egyptian Society for Joint Diseases and Arthritis

The Egyptian Rheumatologist

www.rheumatology.eg.net
www.sciencedirect.com

ORIGINAL ARTICLE

The role of interleukins 4, 17 and interferon gamma as biomarkers in patients with Systemic Lupus Erythematosus and their correlation with disease activity

Enass A. Elewa [a,*], **Omyma Zakaria** [a], **Enas I. Mohamed** [a], **Ghada Boghdadi** [b]

[a] *Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University, Egypt*
[b] *Microbiology and Immunology Department, Faculty of Medicine, Zagazig University, Egypt*

Received 27 July 2013; accepted 2 October 2013
Available online 13 November 2013

KEYWORDS

Systemic Lupus Erythematosus;
Cytokines;
Disease activity (SLEDAI)

Abstract *Aim of the work:* This work was designed to study the production of proinflammatory cytokines in SLE patients and their correlation with disease activity and study if they can be used as biomarkers for renal activity in lupus nephritis patients.

Patients and methods: This study was carried out on 70 subjects divided into two groups: Group I (SLE group) which included 40 SLE patients and Group II (Control group) which included 30 apparently healthy controls. The patients were subjected to full history taking and complete clinical examination. Assessment of disease activity in SLE patients by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Sera of patients and controls were screened for the level of cytokine expression of T helper cells including interleukin 17 (IL-17), interleukin 4 (IL-4) and interferon gamma (IFN-γ).

Results: Serum levels of IL-4 were significantly lower while both IL-17 and IFN-γ were significantly higher in SLE patients than in the control group. The most powerful predictor and correlated cytokine with the SLEDAI in SLE patients was IL-17. Higher serum level of IFN-γ was associated with more pyuria and hematuria, while higher IL-17 was associated with more pyuria and proteinuria in SLE patients.

Conclusion: The serum level of IL-17 and IFN-γ was proven to be significantly higher in SLE patients and can be used as biomarkers of renal activity.

* Corresponding author. Tel.: +20 1229447947.
E-mail address: enassmansour@yahoo.com (E.A. Elewa).
Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.

Production and hosting by Elsevier

1. Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease associated with chronic immune activation and tissue damage that results from the deposition of immune complexes and infiltration of activated T cells into susceptible organs [1].

1110-1164 © 2013 Production and hosting by Elsevier B.V. on behalf of Egyptian Society for Joint Diseases and Arthritis.
Open access under CC BY-NC-ND license. http://dx.doi.org/10.1016/j.ejr.2013.10.003

Cytokines are soluble factors which play a role in differentiation, maturation, and activation of various immune cells. They are not only involved in immune dysregulation of SLE, but also in local inflammatory response leading to tissue injury [2]. These cytokines may exert either pro or anti-inflammatory effects, or both, depending on specific local microenvironment, thus contributing greatly to SLE pathogenesis. Understanding these cytokine abnormalities may be beneficial in developing effective targeting therapeutics [3]. Cytokines play an important role in lupus nephritis, so use of cytokines as biomarkers of disease activity in SLE and lupus nephritis is of particular interest [2]. T cells can be subdivided by the patterns of cytokine released into: (1) Th1 cells produce IL-2 and IFN-γ, which are critical for cell-mediated immunity. (2) Th2 cells produce IL-4, IL-5 and IL-10, which promote antibody production and humoral immunity. (3) Th17 cells produce IL-17 [4].

IFN-γ is generated by both innate and acquired immune cells, particularly T cells and natural killer (NK) cells. It is commonly accepted that IFN-γ can promote Th1 polarization, facilitate specific cytotoxicity by increasing the expression of MHC class-I and -II molecules, and boost antigen processing and immunoglobulin switching [5]. Targeting therapy for IFN-γ has been successfully applied to lupus mice, and treatment with humanized anti-IFN-γ mAb or recombinant IFN-γ-Ig fusion protein may provide a novel therapeutic strategy for this intractable disease in human [6].

IL-4 is a 17 kDa monomeric glycoprotein of the type hematopoietin superfamily secreted by Th2 cells, NK T cells, mast cells and basophils [7]. It plays a central role in regulating the differentiation of antigen-stimulated naive T cells to develop into IL-4-producing Th2 through IL-4R-mediated signaling [8]. IL-4 is a multifunctional cytokine. Although most studies have focused on the B-cell stimulatory and Th2 promoting properties of IL-4 in the development of autoantibodies and autoantibody-mediated diseases, a few reports suggest a T-cell suppressor role for this cytokine in lupus. These properties of IL-4 may sometimes result in opposing outcomes, amplifying or inhibitory, on overall B-cell functions [9].

IL-17 is a type I transmembrane protein isolated initially from a rodent CD4+ T cell DNA library [10]. It is mainly produced by activated Th17 cells which are in fact a subset of CD4+ T lymphocytes named after its hallmark cytokine IL-17. Recent data indicate that IL-17 driven inflammation amplifies SLE-induced tissue damage and contributes to tolerance breakdown in SLE patients [11]. Elevated IL-17 levels in SLE probably contribute to the recruitment and activation of immune cells (e.g., neutrophils and T cells) to target organs and thus amplify immune response [12]. The purpose of this work was to study the production of the cytokines in SLE patients and their correlation with disease activity and study if these cytokines can be used as biomarkers for renal activity in lupus nephritis patients.

2. Patients and methods

This study was carried out in Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University on 70 subjects divided into two groups: Group I (SLE group) which included 40 SLE patients diagnosed according to the American College of Rheumatology (ACR) classification criteria for SLE [13]. Group II (Control group) included 30 apparently healthy controls. Clinical examination as well as routine laboratory investigations confirmed their healthy state. Written informed consent was obtained from all patients and controls for their study participation. The study was approved by the local ethics committee of Zagazig University Hospitals.

2.1. Clinical examination

Patients were subjected to full history taking and complete clinical examination including general, locomotor system, skin, cardiovascular, chest, neurological and vascular examinations.

2.2. Disease activity

The disease activity was assessed in SLE patients by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [14]. Activity categories were defined on the basis of SLEDAI scores [15]; No activity (SLEDAI; 0), Mild activity (SLEDAI; 1–5), Moderate activity (SLEDAI; 6–10), High activity (SLEDAI; 11–19), and Very high activity (SLEDAI; 20).

2.3. Investigations

Investigations included are complete blood picture, erythrocyte sedimentation rate, C-reactive protein, complete urine analysis, 24 h proteinuria, liver and kidney function tests, Complement 3 (Normal value: 87–187 mg/dl), Complement 4 (Normal value: 16–38 mg/dl), ANA, and Anti DNA double stranded antibody (Positive value up to 25 IU/ml).

2.4. Cytokines assay

Blood samples from patients and controls were centrifuged and the sera screened for the level of cytokine expression of T helper cells including interleukin 17, interleukin 4 and interferon gamma (IFN-γ). Sera were analyzed for cytokines by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocols. IL-4 assay by Ani Biotech Oy, Orgenium Laboratories Business Unit, Finland, Product code IL10001, IL04001 and IL13001. Assay range: 15.6–250 pg/ml. IFN-γ assay by Invitrogen, USA, Catalog No. KAC1231. Assay range: 0–1.2 IU/ml. IL-17 assay by WKEA MED supplies, USA. Assay range: 0.5–15 ng/L.

Statistical analysis: It was performed using SPSS statistical software, version 11.0 (SPSS, Chicago, IL). Quantitative variables were given as means ± SD, medians, range and categorical variables in frequencies and percents. *t* Test or the Wilcoxon rank-sum tests were used for continuous variables according to the distribution of the variable and the χ^2-test for categorical variables. Measures the closeness of the association between two quantitative continuous variables by correlation coefficient. Kruskall Wallis one way analysis of variance (KW) test was used to compare median for >2 independent samples that are not related. *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic data of patients and control groups

Demographic data of patients and control groups are presented in Table 1.