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Case Report / Brief Research Article

BAFF as Biomarker to Supervise Corticosteroid Treatment of Precancerous Autoimmune Systemic Lupus Erythematosus disease

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1. Abstract

Aims: The B cell Activating Factor (BAFF) is implicated as a key cytokine in precancerous autoimmune disease of Systemic Lupus Erythematosus, SLE. The objective of the work was to determine the significance of BAFF in SLE glucocorticoid therapy. **Methods & Results**: The study was performed in two groups of patients: 1 - treatment using different dose of glucocorticoids, GCs; 2 - conventional treatment. The BAFF measurement in blood was done using the ELISA method. BAFF values were higher in patients with GCs ≥ 50.0 mg/day, with a mean of 2,844 pg/ml ± 1,495; and in patients with GCs <50.0 mg/day, the mean was 2,422 ± 1,280. The mean BAFF of the control group was 0.990 pg/ml. The difference between these two groups is statistically significant, using the non-parametric Mann Whitney test, with p <0.001. **Discussion & Conclusion**: The immune mechanism of GCs therapy is discussed in the aspect of BAFF related B and T cells, and in coordination with immunotherapy and nanotechnology. Described study constitutes the novel contribution to SLE treatment using the rapid evaluation of serum BAFF level as the biomarker of GCs therapy.

2. *Keywords:* *(MeSH**):** Systemic Lupus Erythematosus Systemic (LES), Glucocorticoids (GCs), B-cell activating* factor *(BAFF), Cytokines, IGF-I, B and T lymphocytes*

3. Abbreviations

SLE: Systemic Lupus Erythematosus; BAFF: B-cell activating factor; GCs: Glucocorticoids; IGF-I: Insulin-like growth factor 1; TGF-beta: Transforming growth factor beta;
IFN-ɣ; interferon gamma; ICAM-1: Intercellular molecular adhesion;
AP-1: Activator protein 1; STAT-4: Signal transducer and activator of transcription 4;
Th1 and Th2: 'Type 1 and 2 T helper: TWEAK: Tumor necrosis factor-like weak;
APRIL: A proliferation inducing factor; CPAs: antigen-presenting cells;
G-CSF: Granulocyte colony-stimulating factor; siRNA: small interfering RNA.
TNF: tumor necrosis factor; NF-KB: nuclear factor kappa B; IL-1: Interleukin 1;

4. Introduction

4.1. Disease: Systemic Lupus Erythematosus

Considering the epidemiology, Systemic Lupus Erythematosus, SLE, is a systemic autoimmune disease characterized by autoantibody production and deposition of immune complexes. The importance of SLE is related to its malignancy being a significant cause of death, affecting predominantly young and middle-aged wome. Thanks to improved detection of minor SLE, the incidence almost tripled in the last 40 years. Estimated incidence rates are up to 25 per 100,000 in North America, South America, Europe and Asia [1].

The risk of malignancy in SLE appears to be related to the immune and genetic pathways [2]. In addition, the presence in SLE of insulin-like growth factor 1 (IGF-I), the most important normal and neoplastic development factor, an inhibitor of apoptosis, in parallel with IGF-II, and the factor 'Transforming growth factor beta' (TGF-beta), as well as especially the activating factor of TNF tumor necrosis factor family B cells (BAFF), are all involved as targets for immunogenic T lymphocyte cells and activation of B lymphocyte cells. These lymphocytes constitute the basis for therapies of autoimmune and cancerous diseases [3-6].

Activated B cells and autoantibody production are a hallmark of SLE. Inversely correlated IGF-1 with B cells, T-CD8 cells (CD8 is a T cell marker) and BAFF, induce an immune response by down regulating B and activating T cells in this pathology [5].

4.2. Treatment: Glucocorticoids

A therapeutic strategy of SLE is associated with the use of glucocorticoids (GCs). The inhibitory activity of GCs is related to the amplification of the inflammatory process by the 'nuclear factor-kappa B' (NF-kB). Inhibition of NF-kB activity by GCs is relevant in anti-inflammatory action resulting in inhibition of inflammatory cytokines of factor TNF-alpha, Interleukin 1 (IL-1) and cytokine interferon gamma (IFN-ɣ) - in relation to 'Intercellular molecular adhesion-1' (ICAM-1), Il-2 and 'Activator protein 1' (AP-1) [7-9].

GCs increase the levels of cytokine interferon beta (IFN-β) and IL-10 induced by the activation of 'Signal transducer and activator of transcription 4 (STAT-4). The effect of GCs on STAT-4 depends on the activation of this signaling pathway. These results may explain the suppressive action of GCs on the cellular immune response 'Type 1 T helper' (Th1) and may help explain the shift towards the humoral immune response Th2 [10,11].

Activation and differentiation of B cells are orchestrated by some members of the TNFα group; three of them are part of this large family: 'Tumor necrosis factor-like weak' (TWEAK) - inducer of apoptosis, 'A proliferation inducing factor' (APRIL) and BAFF [4,6,12]. Pathological excess of BAFF rescues self-reactive B cells from peripheral elimination and provides the microenvironment for further activation [13].

4.3. Objective of the study: BAFF

BAFF is involved as a key cytokine that plays a significant role in autoimmune SLE disease. BAFF is a B-cell activating factor from the tumor necrosis factor family. BAFF is a survival factor for B cells. BAFF has revealed its critical role in B cell proliferation, as well as the pathogenesis of T-cell mediated autoimmune disease. On the other side, BAFF has a role in the survival and/or growth of B-cell lymphomas. Nevertheless, elevated levels

of BAFF have been detected in the serum of patients with various B-cell-mediated autoimmune disorders including precancerous SLE disease.[14]

BAFF is involved in not only the physiology of B cells, but also that of T cells. Both B and T cells play a role in the pathogenesis of autoimmune disease [14]. BAFF induces T cell vitality and activation through the PI3K-Akt signaling pathway [15]**.** The pathway PI3K-AKT related to T cell immunity, plays a principal role in anti-tumor mechanism (for example using anti IGF-1 approach [3])**.** This mechanism is important considering SLE as a precancerous disease.

Our strategy used to modulate BAFF activity may be associated with GCs applied in the treatment of patients. Considering the involvement of BAFF in B and T cells activity, and that of SLE corticosteroid treatment relation with increase of T cell immune response [16], the objective of presented study is to determine how different doses of GCs affect serum levels of BAFF in SLE patients. The BAFF level could play a role in the supervision of corticosteroid treatment in this precancerous disease. Described study is the first one to consider this subject, constituting the novel contribution to diagnosis and therapy of SLE.

5. Materials and Methods

5.1. Patients

The research was carried out with 29 patients, selected in the Service of the Rheumatology (National University of Colombia). The diagnostic parameter was the index of 'Systemic Lupus Erythematosus Disease Activity' (MEX-SLEDAI), applying a score higher than 3 and lower than 12.

The serological tests used to measure lupus activity were serum complement levels (C3, C4, CH50), double-stranded anti DNA antibody levels, antinuclear antibodies (ANAS), extractable nuclear antigens (ENAS) (Ro, La, Sm, RNP), anti nucleosome antibodies, anti ribosomal P, anti cardiolipin antibodies IgG and IgM, anti β2 glycoprotein I type IgG and IgM, according to the subgroup of patients with lupus.

5.2. Study design

The 29 patients selected were divided into two groups, according to the treatment they received: first group - treatment with GCs (21 patients), and second group - conventional treatment (8 patients). The first group was divided into three subgroups, according to glucocorticoids doses as follows: low (<10.0 mg/day), moderate (10.0-49.0 mg/day) and high (50.0 mg/day).

5.3. Samples

After signing the informed consent, each patient underwent direct venopuncture, extracting 5 ml of total blood. The samples were centrifuged at 2,500 revolutions for 5 minutes and stored in 1ml vials in REVCO's cooler at -20.0 °C until the total number of samples for the test was completed.

5.4. Sample processing

The 'enzyme-linked immunosorbent assay' kit (ELISA - Biorbyt Human BAFF ELISA kit, Catalogue No. orb50175), sensitivity <2.0 pg/ml of 96 wells was used for quantitative detection of serum BAFF levels, using Avidin-Biotin-Peroxidase technique and the Vectastain ABC kit (Vector Laboratories, Burlingame, CA, USA). The photometer (photometer) reading was performed using a 450.0 nm filter.

5.5. Statistical analysis

For the statistical analysis, the normality of the BAFF distributions was established in two groups, using the Shapiro Test – Wilk.

In accordance with the above results, the analysis of the information was carried out using descriptive statistics (frequency distributions, means and dispersion measures) and Mann Whitney inferential test, using the SPSS statistical package version 23. The value of p for statistical significance was set at ≤0.05.

5.6. Ethical aspects

This clinical study was conducted in accordance with the Declaration of Helsinki (1975). The clinical trial approval and informed consent was administered by the Bioethics Commission of the National University of Colombia. The anonymous status of participants and the confidentiality of their information are protected by the Faculty of Medicine of the National University of Colombia - Ethics Committee: Authors: Heber Siachoque-Montañez, Milcíades Ibáñez-Pinilla, et al.; Title: 'Defects in zeta-chain expression (ζ) in a group of patients with lupus, scleroderma and late-onset arthritis'; National University, Bogotá, Colombia, October 7, 2013. Published: Rev. Cienc. Salud. 2013;12(3):303-18.

Confidentiality of data: The authors state that they have followed their workplace protocols on the publication of patient data.

Right to privacy and informed consent: Authors have obtained informed advice from patients.

6. Results

6.1. Patients

The distribution of patients who received GCs (21 patients) and those who did not receive GCs (8 patients) was described in 3.2. Study design. The Table 1 shows the distribution of the patients studied: 31.0% received

less than 10.0 mg/day, 20.7% between 10.0 and 49.0 mg/day and 20.7% more than 49.0 mg/day. 27.6% (8 patients) did not receive GCs and were used as a control group.

Table1

6.2. BAFF levels

AS to patients who received GCs, those with the highest levels of BAFF were between 30 and 39 years old. The doses of BAFF that are most frequently released are found in a concentration between 1,000 and 1,999 pg/ml (Table 1); it is noted that, if GCs was not administered, no concentrations above 2,000 pg/ml were reported (Table 2). The figure shows the maximum and minimum values (the values of the 75th and 25th percentiles and the media).

Table2

6.3. BAFF and Glucocorticoids

The Table 3 and the Table 4 present the mean BAFF: for the first group, the values ranged between 2,844 pg/ml in patients who received more than 49.0 mg/day, and 2,280 pg/ml in those who received less than 10.0 mg/day, with an overall average of 2,482 pg/ml.

An analysis of variance, with the limitations of normality presented by the distributions, showed that the differences are statistically significant with a $p = 0.022$. In the control group, the mean BAFF was significantly lower by 0.990 pg/ml.

Using the Mann Whitney test, it was established that the difference between the values of the group that received GCs and the group that did not receive them is statistically significant, with with a $p = <0.001$.

Table 3

Table 4

6.4. Data availability statement

The presented datasets are not readily available because of ethical consent for patients. All reported molecular biology and immunology aspects of BAFF are already described in the literature. Requests to access the datasets should be directed to corresponding authors and clinician Hebert O. Siachoque.

7. Discussion and Conclusion

The obtained results have demonstrated a very significant relation between GCs treatment and serum BAFF levels. There was a clear trend of higher BAFF values with higher doses of GCs in relation to cytokines (Table 3 and Table 4).

An explanation for the increase in BAFF related to the use of GCs would be associated with important events as follows. The BAFF synthesis induced in antigen-presenting cells (CPAs) is done through pro-inflammatory stimuli: interferons type I (α, β) and interferons type II (ɣ) and interleukin-10 (IL-10), and also other factors such as 'Granulocyte colony-stimulating factor' (G-CSF) and dendritic cells [17]. Then an increase in lupus activity happens, in which activated antigen-presenting cells release cytokines such as INF-ɣ, IL-10, IL-12, following by a higher BAFF synthesis [17,18]. The action of GCs and transcriptional modifications induced by cytokines such as i.e. INFs and IL-10 may be involved in transcriptional modifications involving synthesis of factors such as BAFF [19-21].

SLE may be associated with an increased risk of malignant tumors such as liver, colon cancer, or leukemia [22]. The probable link involves IGF-I as a general stimulant, synergized by multiple inflammatory cytokines (i. e. TNF). Moreover, the pathogenesis of SLE could be related to viral causes, immune and genetic pathways and immunosuppressive drugs [2, 23].

The treatment of other diseases including use of GCs has been introduced in clinical trials. The efficient treatment of precancerous and malignant diseases was done using inhibitors targeting IGF-I, especially the IGF-I antisens and triple helix technologies [23]. The GCS are applied as the first step of this therapy. The mechanism of this strategy is accompaned by the presence of CD8 T cells. In another strategy of GCs therapy published recently, the authors have demonstrated that the patients treated for tumor disease (glioma), receiving exclusively exceded doses of GCs, presented a high CD8 T cell expression and SRC-1 gene down regulation [**16**]. In general, using GCs tretaement, the increased median survival of patients has occured in all mentioned therapies. Moreover, considering the presence

of activated T and B cells in GCS therapies, both lymphocyrz population play together a role in anti-tumort response [24].

On the other side, nanotechnology has emerged as a promising field to improve both the diagnosis and treatment of SLE, and enabling targeted delivery of glucocorticoids; one promising approach involves the use of nanoparticles to deliver small interfering RNA (siRNA) molecules that target specific genes involved in SLE pathogenesis maximizing therapeutic efficacy. As to the diagnosis, gold nanoparticle-based biosensors could detect different molecules including BAFF in serum samples from SLE patients {25,26].

In conclusion we underline that the article presents preliminary original results of a scientific / clinical research on a new way to supervise SLE therapy. This work has shown a compilation of the most relevant and current treatments of SLE with GCs. The results of our clinical observations should be considered as personal medicine treatment due to the consideration of relation between BAFF and GCs levels. The presented results have demonstrated that therapy with GCs is associated with a marked tendency to increase serum levels of BAFF using higher doses of GCs. Finally, the BAFF level value has become the diagnostic marker in this type of SLE therapy.

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9. Conflict of interests

Authors declare no conflict of interest

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Tables:

Table 1

Age groups	**Levels of BAFF concentration**				**Total**
(years)	<1,000 pg/ml	1,000-1,999 pg/ml	2,000-2,999 pg/ml	>3,000 pg/ml	
Menores de 30	0	2	1	1	4
30 a 39	0	3	3	1	**7**
40 a 49	1	1	0	2	4
50 and more	0	3	1	2	6
Total	1	9	5	6	21

Table 1: *Distribution of the studied patients, according to the dose of glucocorticoid. Considering 21 patients treated with corticosteroids, 31.0% received less than 10 mg/day, 20.7% between 10.0 and 49.0 mg/day and 20.7% more than 49.0 mg/day. The group of 27.6% (8 patients) did not receive corticosteroids and constitute a control group. BAFF concentration levels was measured in pg/ml; BAFF levels increased to a concentration between 1,000 and 2,999 pg/ml.*

Table 2

Age groups (years)	**Levels of BAFF concentration**		**Total**
	< 1,000 pg/ml	1,000 - 1,999 pg/ml	
<30	3	2	5
30- 39	0	2	2
>50	1	0	1
Total	4	4	8

Table 2: *Serum BAFF concentration levels by age group. No concentrations above reported 2,000 pg/ml. See Results (BAFF levels).*

Table 3

Dose of corticosteroids	Median value BAFF (pg/ml)	Patients	Standard deviation
< 10.0 mg/day	2,278	9	1,10
10.0-49.0 mg/day	2,422	6	1,281
>50.0 mg/day	2,844	6	1,494
0,0 mg/day	0,990	8	0,439

Table 3: *BAFF concentration levels measured in pg/ml, according to dose of corticosteroids received.*

Table 4

Groups of treatment	Patients	Median value	Standard deviation	Median value of standard error
Therapy with corticosteroids	21	2,482	1,230	0,268
Therapy without corticosteroids	8	0, 990	0,439	0,155

Table 4: *BAFF concentration levels in pg/ml, according to treatment groups. Mann Whitney test for differences between means p < 0.001*