

## Serum B-Cell Activating Factor (BAFF) and Sarcoidosis Activity

Kamila HASHEMZADEH<sup>1</sup>, Maryam FATEMIPOUR<sup>1</sup>, Seyede ZAHRA MIRFEIZI<sup>1</sup>,  
Mohammadhasan JOKAR<sup>1</sup>, Zhaleh SHARIATI SARABI<sup>1</sup>, Mohammad-Reza HATEF FARD<sup>1</sup>,  
Houshang RAFATPANAHI<sup>2</sup>, Mandana KHODASHAHI<sup>1</sup>

<sup>1</sup>Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>2</sup>Department of Inflammation and Inflammatory Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

### ABSTRACT

**Objectives:** This study aims to determine the relationship between the severity of sarcoidosis and serum B-cell activating factor (BAFF) concentrations.

**Patients and methods:** This cross-sectional study was conducted between December 2015 and March 2018 on 55 patients with sarcoidosis (16 males, 39 females; mean age, 39.9; range 25 to 60 years) and 28 healthy subjects (7 males, 20 females; mean age, 39; range 25 to 60 years). The sarcoidosis patients were divided into active chronic sarcoidosis and acute sarcoidosis groups. The diagnosis of sarcoidosis was based on clinical, radiological, and pathologic findings. Also, the diagnosis of the active disease was based on the level of angiotensin-converting enzyme, active skin, eye, and lung lesions. Scadding score was also measured, and other patient information was collected by pre-designed questionnaires.

**Results:** The most involved organs were the skin (92.7%) and joints (92.3%), respectively. The mean BAFF concentration in both active chronic sarcoidosis ( $p=0.001$ ) and acute sarcoidosis ( $p=0.001$ ) groups was significantly higher than the control group, but the mean level of BAFF in these two groups was not significantly different ( $p=0.351$ ). Between two groups of patients, only calcium ( $p=0.001$ ) and forced vital capacity ( $p=0.021$ ) were higher in the acute group of sarcoidosis. Also, among the factors associated with active chronic sarcoidosis and acute sarcoidosis, none was significantly correlated with BAFF.

**Conclusion:** Serum BAFF concentration was higher in patients with sarcoidosis, while this was not significantly different from increasing severity of symptoms. There was no significant difference in BAFF levels between acute sarcoidosis and active chronic types.

**Keywords:** B-cell activating factor, biomarker, sarcoidosis.

Sarcoidosis is a multi-system granulomatous disease with an unknown cause.<sup>1</sup> Lungs are the most involved organs in the disease. Other organs that can be involved include eyes, skin, muscles, liver and joints.<sup>2</sup> Though T cells play a significant role in the development of sarcoidosis, researches have shown that the humoral immune response can contribute to the disease.<sup>3,4</sup> Aggregation of B cells and plasmatic hypergammaglobulinemia are seen in pulmonary lesions, while positive effects

of monoclonal antibodies (anti-CD20) have been reported in patients.<sup>4,5</sup>

B cells are commonly known as a positive immune stimulant in inflammation. B cell-activating factors (BAFFs), which are a family of tumor necrosis factors, play a vital role in the growth and function of B cells, so that their inhibition dramatically reduces the number of B cells in the follicular and marginal regions.<sup>6</sup> Also,

**Received:** January 21, 2020 **Accepted:** April 07, 2020 **Published online:** September 11, 2020

**Correspondence:** Mandana Khodashahi, MD. Rheumatic Diseases Research Center (RDRC), Ghaem Hospital, Ahmad-Abad Ave., Dr Shariati Sq., 9176699199 Mashhad, Razavi Khorasan, Iran. Tel: +985138012753 e-mail: Khodashahim@mums.ac.ir

### Citation:

Hashemzadeh K, Fatemipour M, Zahra Mirfeizi S, Jokar M, Shariati Sarabi Z, Hatf Fard MR, et al. Serum B-Cell Activating Factor (BAFF) and Sarcoidosis Activity. Arch Rheumatol 2021;36(x):i-viii.

increasing the expression of BAFF in mice causes the development of reactive cells, as well as the production of autoimmune antibodies.<sup>7</sup>

The active form of the disease means that T cells and macrophages are still active, and granuloma tissues are associated with an ongoing illness. In contrast, the inactive form of the disease is when the disease does not find any progress.<sup>8</sup> Factors such as angiotensin-converting enzyme (ACE) and lysosomal that are produced by the epithelial and giant cells can be indicative of the activation and progression of the disease.<sup>9</sup> In this study, we aimed to determine the relationship between the severity of sarcoidosis and serum BAFF concentrations.

## PATIENTS AND METHODS

This cross-sectional study was conducted at Mashhad University of Medical Sciences Faculty of Medicine/Imam Reza Hospital between December 2015 and March 2018 on 55 patients with sarcoidosis (16 males, 39 females; mean age, 39.9; range 25 to 60 years) and 28 health controls (7 males, 20 females; mean age, 39; range 25 to 60 years). Inclusion criteria were patients who had a history of sarcoidosis based on pathological, clinical and laboratory criteria, while exclusion criteria were a history of steroid therapy due to other internal diseases, pregnancy, renal failure, liver and heart failure, patient dissatisfaction with the continuation of the study, cancer and history of chemotherapy, other rheumatologic diseases, immunodeficiency, coagulation disorders, smokers, alcoholics and malnourished patients. The study protocol was approved by the Mashhad University of Medical Sciences Faculty of Medicine/Imam Reza Hospital Ethics Committee. A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Sarcoidosis patients were divided into two as active chronic sarcoidosis (n=26) and acute sarcoidosis (n=29) groups. The sampling method was convenience sampling and all patients referred to the rheumatology clinic of the university hospital with a diagnosis of sarcoidosis were included. The diagnosis of sarcoidosis was based on clinical, radiological, and pathologic findings,

and the diagnosis of the type of disease was based on the level of ACE, active skin, eye and lung lesions. Patients with acute sarcoidosis were prescribed according to the Visser criteria: patients with three or four symptoms of age below 40 years, erythema nodosum, sympathetic arthritis in both elbows and a period of illness of less than two months were placed in the acute group of sarcoidosis while the other patients were included in the active chronic sarcoidosis group.<sup>10</sup>

In this study, 5 mL of blood was collected from the brachial vein by a qualified nurse from patients and controls. At this point, the co-worker noted that the tourniquet should not be closed for long periods. The blood sample was prepared in a non-solid state and then centrifuged at 3,000 rpm for 10 minutes. It was stored at -80°C, then BAF levels were measured by enzyme-linked immunosorbent assay while serum immunoglobulin (Ig) G, IgM, and IgA were measured by nephelometric process. Also, samples' calcium, C-reactive protein, erythrocyte sedimentation rate and ACE levels were measured. Other patient information such as age, sex and duration of the disease was obtained by pre-designed questionnaires.

### Statistical analysis

An alpha error of 5% and a beta error of 20% were considered. A comparison of the mean and standard deviation of the control group and sarcoidosis groups was performed for BAFF, which was sufficient for 20 samples in each group. Considering that we had three groups for comparison in the present study, the sample size was multiplied by coefficient  $\sqrt{2}$ , which increased the sample size to 28 persons in each group. Statistical analysis was performed by the PASW version 18.0 software (SPSS Inc., Chicago, IL, USA). Chi-square and Fisher's exact tests were used for nominal variables. For independent comparison, data independent of the T-test (parametric) were used. The significance level for statistical analyses was considered as 5%.

## RESULTS

In this study, the majority of the patients were female (70.9%) and the duration of disease was

**Table 1.** Demographic information and frequency of different organ involvements in active chronic sarcoidosis and acute sarcoidosis

Variable	Control (n=27)			Active chronic sarcoidosis (n=26)			Acute sarcoidosis (n=29)			Total (n=82)			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (year)*			7.0±39.0			11.3±41.8			8.9±38.2			9.2±39.6	0.33
Sex**													0.90
Male	7	25.9		7	26.9		9	31		23	28		
Female	20	74.1		19	73.1		20	69		59	72		
Lung involvement	-	-		26	100		29	100		-	-		-
Articular involvement	-	-		19	73		29	100		-	-		-
Ocular involvement	-	-		8	30.8		5	17.2		-	-		-
Skin involvement	-	-		22	84.6		29	100		-	-		-
Gastrointestinal involvement	-	-		2	7.7		-	-		-	-		-
Kidney involvement	-	-		-	-		-	-		-	-		-
Thoracic lymphadenopathy	-	-		2	7.7		-	-		-	-		-
Breast involvement	-	-		1	2.8		-	-		-	-		-
Parotid involvement	-	-		-	-		-	-		-	-		-
Splenomegaly	-	-		4	15.4		-	-		-	-		-
Heart involvement	-	-		6	23		-	-		-	-		-

SD: Standard deviation; \* Analysis was performed by ANOVA test; \*\* Analysis was performed by Chi-square; ANOVA: Analysis of variance.

**Table 2.** Relationship between B-cell activating factor values and disease manifestations

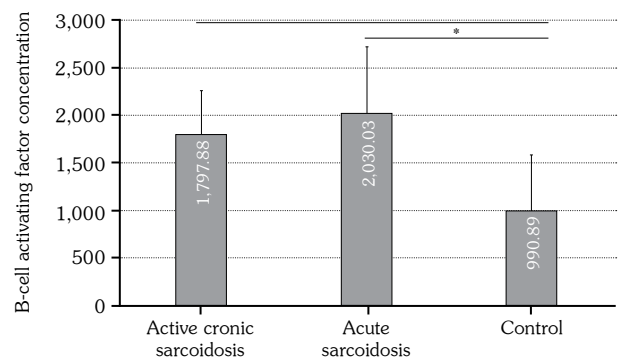
Variable	n	%	BAFF	
			Mean±SD	p
Type of disease*				0.351
Active chronic sarcoidosis	26	47.3	1,797.9±464.9	
Acute sarcoidosis	29	52.7	2,030.0±688.5	
Sex*				0.689
Female	39	70.9	1,899.3±664.6	
Male	16	29.1	1,971.6±413.9	
Ocular manifestation*				0.149
Normal	42	76.4	1,965.6±650.8	
Anterior uveitis	13	23.6	1,773.9±374.8	
Skin manifestation**				0.846
Normal	4	7.3	1,785.8±758.3	
Erythema nodosum	46	83.6	1,920.9±615.3	
Papule and macule	5	9.1	2,022.6±363.2	
Palpation	3	5.5	1,486±474.6	
Scadding score**				0.379
BHL	46	83.6	1,961.1±603.4	
BHL and pulmonary infiltration	7	12.7	1,846.6±563.3	
Pulmonary infiltration	1	1.8	1,449.00	
Pulmonary fibrosis	1	1.8	1,031.00	
Articular manifestation**				0.343
Normal	7	12.7	2,074.5±728.7	
Arthritis	22	40	1,874.0±471.7	
Peri-arthritis	19	34.5	1,621±583.6	
Arthralgia	7	12.7	1,860.7±408.4	
HRCT manifestation**				0.379
Mediastinal lymphadenopathy	46	83.6	1,961.1±603.4	
Increased interlobar septum wall thickness	7	12.7	1,846.6±563.3	
Increased bronchial, interlobar septum wall thickness and reticulonodular pattern	1	1.8	1,449.00	
Bronchiectasis and fibrosis	1	1.8	1,031.00	

BAFF: B-cell activating factor; SD: Standard deviation; BHL: Bilateral Hilar Lymphadenopathy; HRCT: High-resolution computed tomography; \* Analysis performed by two-sample independent t-test; \*\* Analysis performed by ANOVA; ANOVA: Analysis of variance.

more than two months in most of them. Among the symptoms of the disease, the most extrapulmonary symptoms were erythema nodosum (n=46, 83.6%), arthritis (n=22, 40%) and anterior uveitis (n=13, 23.6%). Other patient related information is shown in Table 1.

The BAFF levels in males and females were not significantly different. The mean BAFF concentration in both active chronic sarcoidosis (p=0.001) and acute sarcoidosis (p=0.001) groups was significantly higher than the control group, while the mean concentration of BAFF in these two groups was not significantly different (p=0.351). BAFF level was not significantly different in different manifestations of the disease (Table 2). Figure 1 shows BAFF concentration between active chronic sarcoidosis, acute sarcoidosis, and control groups.

Table 2 shows the BAFF score in each of the various manifestations of the disease. BAFF concentration did not differ significantly in any



**Figure 1.** Comparison of B-cell activating factor concentration between active chronic sarcoidosis, acute sarcoidosis and control groups.

**Table 3.** Comparison between active chronic sarcoidosis and acute sarcoidosis

Variable	Active chronic sarcoidosis		Acute sarcoidosis		p
	n	Mean±SD	n	Mean±SD	
Age (year)	26	41.8±11.3	29	38.2±8.9	0.778
Angiotensin-converting enzyme (UI/dL)	26	80.8±47.0	29	75.7±28.4	0.622
B-cell activating factor (ng/L)	26	1,797.9±464.9	29	2,030.0±688.5	0.351
Calcium (Mg/dL)	26	9.6±0.6	29	9.1±0.3	0.001*
Erythrocyte sedimentation rate (mm/hr)	26	38.2±31.5	29	49.7±21.8	0.128
C-reactive protein (mg/dL)	26	36.8±39.9	29	55.2±44.2	0.112
IgG (Unit)	26	1,210.7±370.7	29	1,359.7±369.3	0.142
IgM (Unit)	26	117.0±53.4	29	152.2±112.3	0.151
IgA (Unit)	26	301.0±119.0	29	356.8±126.0	0.098
FEV1	26	83.0±17.8	29	90.8±9.4	0.055
FVC	26	90.4±15.7	29	98.2±4.0	0.021*
FEV1:FVC	26	0.9±0.1	29	0.9±0.1	0.276

SD: Standard deviation; Ig: Immunoglobulin; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; \* Significance level was p<0.05.

of the ocular, skin, and other symptoms of the disease. Also, laboratory factors were compared between the two groups, among which the level of calcium in the group of active chronic sarcoidosis was significantly higher than that of acute sarcoidosis (9.6±0.6 vs. 9.1±0.3; p<0.001). Also, the forced vital capacity (FVC) was markedly lower in the group of active chronic sarcoidosis

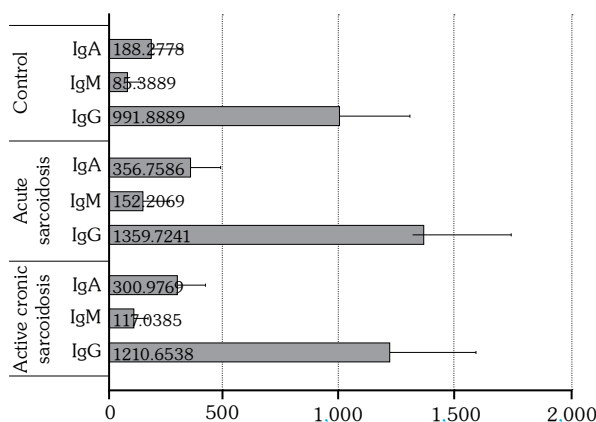
(90.4±15.7 vs. 98.2±4.0; p=0.021). Other factors were not significantly different between the two groups (Table 3).

Among the factors associated with active chronic sarcoidosis and acute sarcoidosis, none was significantly correlated with BAFF (Table 4). Figure 2 shows the mean of serum Ig

**Table 4.** Comparison of correlation between B-cell activating factor levels in serum and laboratory markers, including serum markers of disease activity and pulmonary function tests in active chronic sarcoidosis and acute sarcoidosis

Variable	Active chronic sarcoidosis			Acute sarcoidosis		
	n	p	Pearson correlation	n	p	Pearson correlation
Angiotensin-converting enzyme (UI/dL)	26	0.467	0.149	29	0.237	0.227
Calcium (Mg/dL)	26	0.777	-0.058	29	0.983	0.004
Erythrocyte sedimentation rate (mm/hr)	26	0.18	0.271	29	0.765	0.058
C-reactive protein (mg/dL)	26	0.914	-0.022	29	0.235	0.228
IgG (Unit)	26	0.987	0.003	29	0.541	0.118
IgM (Unit)	26	0.799	0.052	29	0.085	-0.326
IgA (Unit)	26	0.817	-0.048	29	0.051	0.365
FEV1¶	26	0.83	0.044	29	0.81	0.047
FVC¶	26	0.804	0.051	29	0.387	0.167
FEV1:FVC	26	0.868	-0.026	29	0.954	-0.011

FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; Ig: Immunoglobulin.



**Figure 2.** Mean serum immunoglobulin concentration in active chronic sarcoidosis, acute sarcoidosis and control groups.

concentrations in patients and controls. There was no significant difference between the patients with acute sarcoidosis and active chronic sarcoidosis in terms of IgA ( $p=0.098$ ), IgG ( $p=0.142$ ), and IgM ( $p=0.151$ ) levels. Statistical analysis with two-sample independent t-test showed that there was a significant difference between IgG and the control group ( $p=0.001$ ), while there was no difference in active chronic sarcoidosis and control group ( $p=0.065$ ). Also, IgM concentration in control and acute sarcoidosis groups had a statistically significant difference ( $p=0.007$ ), but IgM concentration was not significantly different between active chronic sarcoidosis and control groups ( $p=0.237$ ). For IgA, there was a significant difference between the controls and active chronic sarcoidosis ( $p=0.005$ ) and acute sarcoidosis ( $p=0.001$ ) groups.

## DISCUSSION

In this study, which was performed on 55 patients with sarcoidosis, after the pulmonary involvement, the most involved organs were skin, eyes, and joints, respectively. The mean serum BAFF concentration was significantly higher in the two groups of active chronic sarcoidosis and acute sarcoidosis than the control group. Still, the mean of BAFF in two patient groups was not significantly different. Among the active chronic sarcoidosis and acute sarcoidosis groups, only calcium and FVC levels were statistically

different, which was more common in the active sarcoidosis. Other findings of our study indicate that among the factors associated with active chronic sarcoidosis and acute sarcoidosis, none was significantly correlated with BAFF.

Many studies point out the role of B cells in the pathogenesis of sarcoidosis.<sup>11,12</sup> BAFF is an essential factor in regulating the humoral immune system, the maturation of B cells, as well as in dividing the B cells and preventing their apoptosis.<sup>12,13</sup> This factor leads to the differentiation of B cells into Ig-producing plasma cells.<sup>14</sup> Previous studies have shown that serum BAFF levels are associated with the activity of sarcoidosis.<sup>2</sup> Our study also had similar results, and serum BAFF levels were significantly higher in the patients than controls. Studies show that in some autoimmune diseases such as lupus erythematosus and rheumatoid arthritis, BAFF level is higher than a healthy population.<sup>15</sup> In a clinical trial study at phase 3, belimumab, an inhibitor of BAFF, could reduce symptoms in patients with lupus.<sup>16</sup> Therefore, it seems that the use of this drug for patients with sarcoidosis can also be effective and safe. In this study, we attempted to demonstrate if BAFF concentrations could indicate the severity of the disease in addition to the activity of sarcoidosis.

In a study by Ando et al.,<sup>2</sup> the increased ACE and lysosomal levels, as two predictors of the severity of the disease, had a positive correlation with BAFF. In another study by Saussine et al.,<sup>12</sup> there was a significant relationship between BAFF serum levels and severity of illness as well as hypergammaglobulinemia. They found that there was no significant correlation between the subtypes of B cells and the disease in inactive type unlike acute and chronic types. In our study, there was no significant correlation between the ACE and BAFF values.

The severity of sarcoidosis is usually based on criteria which include radiographic findings, pulmonary function tests and evaluation of extrapulmonary involvement.<sup>17</sup> Laboratory findings that have been presented in previous studies to evaluate the severity of the disease include ACE, soluble interleukin-2 receptor, C-X-C motif chemokine ligands 9 and 10.<sup>18-21</sup> In another survey of BAFF, there was a significant relationship between this factor and the degree of progression of the disease

in radiographic images and the extent of the involvement of other organs of communication.<sup>2</sup> The difference in our study from previous studies was that to our knowledge for the first time, a comparison was performed between patients with acute sarcoidosis or Lofgren syndrome and patients with active chronic sarcoidosis, which revealed no significant difference in serum BAFF concentrations between the two groups.

This study has some limitations. Due to small sample size, affecting outcome by uncontrolled intervention variables, and the retrospective nature of study, we cannot generalize our findings. Therefore, it is suggested that future researchers carry out further studies with large sample size to check the results obtained from our study.

In conclusion, serum BAFF concentrations were higher in patients with sarcoidosis in comparison to a healthy population, while there was no significant relationship between severity and duration of disease and serum levels of BAFF. We also found no significant difference in BAFF levels between acute and active chronic types of sarcoidosis. Due to the high serum BAFF levels in patients with sarcoidosis and its role in the pathogenesis of the disease, in addition to diagnosis, it can be suggested that BAFF inhibitor compounds can be used as treatments in sarcoidosis while further studies are needed in this regard. However, this study has attempted to question the use of serum BAFF to predict the severity of disease.

#### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

#### Funding

The authors received no financial support for the research and/or authorship of this article.

## REFERENCES

- Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011;305:391-9.
- Ando M, Goto A, Takeno Y, Yamasue M, Komiya K, Umeki K, et al. Significant elevation of the levels of B-cell activating factor (BAFF) in patients with sarcoidosis. *Clin Rheumatol* 2018;37:2833-8.
- Fazel SB, Howie SE, Krajewski AS, Lamb D. B lymphocyte accumulations in human pulmonary sarcoidosis. *Thorax* 1992;47:964-7.
- Becker-Merok A, Nikolaisen C, Nossent HC. B-lymphocyte activating factor in systemic lupus erythematosus and rheumatoid arthritis in relation to autoantibody levels, disease measures and time. *Lupus* 2006;15:570-6.
- Dasilva V, Breuil V, Chevallier P, Euler-Ziegler L. Relapse of severe sarcoidosis with an uncommon peritoneal location after TNFalpha blockade. Efficacy of rituximab, report of a single case. *Joint Bone Spine* 2010;77:82-3.
- Rauch M, Tussiwand R, Bosco N, Rolink AG. Crucial role for BAFF-BAFF-R signaling in the survival and maintenance of mature B cells. *PLoS One* 2009;4:e5456.
- Stohl W, Xu D, Kim KS, Koss MN, Jorgensen TN, Deocharan B, et al. BAFF overexpression and accelerated glomerular disease in mice with an incomplete genetic predisposition to systemic lupus erythematosus. *Arthritis Rheum* 2005;52:2080-91.
- Pertschuk LP, Silverstein E, Friedland J. Immunohistologic diagnosis of sarcoidosis. Detection of angiotensin-converting enzyme in sarcoid granulomas. *Am J Clin Pathol* 1981;75:350-4.
- Lawrence EC, Brousseau KP, Berger MB, Kurman CC, Marcon L, Nelson DL. Elevated concentrations of soluble interleukin-2 receptors in serum samples and bronchoalveolar lavage fluids in active sarcoidosis. *Am Rev Respir Dis* 1988;137:759-64.
- Visser H, Vos K, Zanelli E, Verduyn W, Schreuder GM, Speyer I, et al. Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis* 2002;61:499-504.
- Ueda-Hayakawa I, Tanimura H, Osawa M, Iwasaka H, Ohe S, Yamazaki F, et al. Elevated serum BAFF levels in patients with sarcoidosis: association with disease activity. *Rheumatology (Oxford)* 2013;52:1658-66.
- Saussine A, Tazi A, Feuillet S, Rybojad M, Juillard C, Bergeron A, et al. Active chronic sarcoidosis is characterized by increased transitional blood B cells, increased IL-10-producing regulatory B cells and high BAFF levels. *PLoS One* 2012;7:e43588.
- Mackay F, Browning JL. BAFF: a fundamental survival factor for B cells. *Nat Rev Immunol* 2002;2:465-75.
- Do RK, Hatada E, Lee H, Tourigny MR, Hilbert D, Chen-Kiang S. Attenuation of apoptosis underlies B lymphocyte stimulator enhancement of humoral immune response. *J Exp Med* 2000;192:953-64.
- Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum* 2001;44:1313-9.
- Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:721-31.

17. Popević S, Šumarac Z, Jovanović D, Babić D, Stjepanović M, Jovičić S, et al. Verifying Sarcoidosis Activity: Chitotriosidase versus ACE in Sarcoidosis - a Case-control Study. *J Med Biochem* 2016;35:390-400.
18. Rothkrantz-Kos S, van Diejen-Visser MP, Mulder PG, Drent M. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003;49:1510-7.
19. Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JM, van Velzen-Blad H. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. *Chest* 2003;124:186-95.
20. Su R, Nguyen ML, Agarwal MR, Kirby C, Nguyen CP, Ramstein J, et al. Interferon-inducible chemokines reflect severity and progression in sarcoidosis. *Respir Res* 2013;14:121.
21. Bargagli E, Bianchi N, Margollicci M, Olivieri C, Luddi A, Coviello G, et al. Chitotriosidase and soluble IL-2 receptor: comparison of two markers of sarcoidosis severity. *Scand J Clin Lab Invest* 2008;68:479-83.