Immunology Letters 211 (2019) 23–27

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Lack of association between serum IL-9 levels and Behçet's disease

Masoud Nouri-Vaskeh, Aida Malek Mahdavi*,[1], Alireza Khabbazi*,[1], Golamreza Jadideslam

Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Keywords:
Behçet's disease
Interleukin-9
Disease activity

ABSTRACT

Introduction: Considering the role of interleukin (IL)-9 and IL-9-producing Th9 cells in pathogenesis of autoimmune diseases, this study aimed to evaluate serum IL-9 levels in patients with Behçet's disease (BD) compared to healthy subjects and to assess whether there is an association between serum IL-9 levels and disease characteristics in BD.

Methodology: In this cross-sectional study, 32 BD patients according to the International Criteria for BD (ICBD) and 56 age-matched healthy controls were included. In patients, clinical examination was performed and Behcet's Disease Current Activity Form (BDCAF), Iranian Behcet's Disease Dynamic Activity Measure (IBDDAM) and Total Inflammatory Activity Index (TIAI) were assessed. Serum IL-9 level was measured using ELISA kit.

Results: The mean ± SD age of patients and controls was 39.06 ± 9.86 and 38.64 ± 8.40 years, respectively and 41% of patients and 66% of controls were males. The most common clinical symptoms in BD patients were oral aphthous ulcers, ocular involvement, and genital ulcers, respectively. The median (Min–Max) of BDCAF, IBDDAM and TIAI in patients were 2 (0–4), 1.3 (0–7), and 2 (0–22), respectively. There was no significant difference in serum IL-9 levels between BD patients (47.12 ± 7.34 mg/dL) and healthy controls (48.61 ± 7.76 mg/dL) ($P > 0.05$). There were no significant correlations between serum IL-9 levels with BD clinical characteristics as well as with disease severity ($P > 0.05$).

Conclusion: Our study revealed no significant difference in serum IL-9 between BD patients and healthy controls as well as no significant correlation between serum IL-9 with clinical characteristics and disease severity. Further studies are certainly needed, but on a wider cohort of BD patients to identify IL-9 involvement in BD pathogenesis.

1. Introduction

Behcet's disease (BD) is a chronic multisystem autoinflammatory disease characterized by recurrent oral and genital aphthous ulcers, skin lesions, uveitis as well as articular, gastrointestinal, neurologic, and vascular features [1]. BD may be distributed worldwide, but it is more common in Asian and Mediterranean regions especially along the Old Silk Road such as Turkey, Iran, China, and Japan [1]. The etiology and pathogenesis of BD is unclear; however, both autoimmune and inflammatory syndromes have been indicated in the pathogenesis of BD, perhaps prompted by infections or other environmental factors [2,3]. The main pathology in BD is an inflammatory process of small arteries and veins and thrombosis as a consequence of vasculitis [4]. It is well known that acute phase proteins are lower in BD than in other rheumatic diseases and they do not correlate with disease activity or clinical manifestations [5]. Due to the activation of the immune system, cytokines, and inflammatory mediators can modulate the disease process [6]. It has been assumed that a malicious cycle of cytokine network originating from innate immune cells and expanding to T helper (Th) cells plays role in BD pathogenesis [7]. Th cells functionally differentiate into various subsets such as Th1, Th2, Th17, and regulatory T cells (Tregs), which are involved in development and progression of inflammatory and autoimmune diseases [8]. In BD, there is an interleukin 6 (IL-6), tumor necrosis factor (TNF)-α and Th17 pathway that could discriminate patients with different organ involvement [9,10]. Recently, a new T-cell subset has been identified as Th9 cells that mainly secrete the interleukin 9 (IL-9) [8]. IL-9 is a protein of 144 amino acids with a secretory signal sequence of 18 amino acids [11]. It is a pleiotropic cytokine which exerts its various biologic effects on multiple types of cells and different tissues through IL-9R, a cC-family receptor [12]. On target cells, IL-9 binds to IL-9R, a heterodimeric protein composed by IL-9Ra belonging to the haematopoietin superfamily, and the IL-2R-g, a common subunit shared by different cytokine receptors. Binding of IL-9 with the cognate receptors

* Corresponding authors at: Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Golgasht St., P.O Box 5166614756, Tabriz, Iran.
E-mail addresses: aidamalek@gmail.com (A. Malek Mahdavi), dr_khabbazi@yahoo.com (A. Khabbazi).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.imlet.2019.05.007
Received 2 April 2019; Received in revised form 1 May 2019; Accepted 12 May 2019
Available online 13 May 2019

leads to the activation of signal transducer and activator of transcription-1 (STAT-1), STAT-3 and STAT-5 [12]. Th9 cells and IL-9 are usually proinflammatory, but they also have some anti-inflammatory characteristics [8]. Recently, IL-9 has been shown to play a key role in the pathophysiology of various autoimmune diseases, such as rheumatoid arthritis (RA) [13], psoriasis [14], atopic dermatitis [15–17], systemic lupus erythematosus (SLE) [18], lupus nephritis [19], systemic sclerosis (SSc) [20], type 1 diabetes mellitus [21], and multiple sclerosis [22]. Furthermore, IL-9 has been studied in different animal models of autoimmune disease, such as lupus-prone mice [23], experimental autoimmune encephalomyelitis [24,25], experimental autoimmune uveitis [26], and experimental autoimmune myasthenia gravis [27]. Most recently, in patients with giant cell arteritis (GCA) classified as a large vessel vasculitis according to the revised Chapel Hill Criteria [28], IL-9 overexpression and Th9 polarization were reported in arteries with transmural inflammation and small-vessel vasculitis [29]. The tissue expression of IL-9 was correlated with the intensity of the systemic inflammatory response, and IL-9R was also overexpressed in the GCA patients arteries [29]. In addition, it was shown that serum IL-9 levels and peripheral blood Th9 cells were significantly higher in patients with Takayasu's arteritis (TAK), another type of large vessel vasculitis, compared to healthy controls and the levels of IL-9 had a significant positive correlation with erythrocyte sedimentation rate (ESR) in these cases [30]. These data suggests that Th9 cells and IL-9 play an important role in autoimmune response of TAK and could possibly be involved in the pathogenesis of TAK [30]. BD is also considered a "variable vessel vasculitis" based on the revised Chapel Hill Criteria [28], however the role of Th9 or IL-9 in BD has yet to be investigated. The purpose of this study was to evaluate the serum levels of IL-9 in patients with BD compared to healthy subjects and to assess the association between serum IL-9 levels and clinical manifestations of BD.

2. Materials & methods

2.1. Subjects

In this case-control study, patients older than 16 years of age with the diagnosis of BD according to the International Criteria for BD (ICBD) [31] which has higher sensitivity, specificity and accuracy than International Study Group (ISG) criteria [32,33], were recruited consecutively from the outpatient rheumatology clinic of Tabriz University of Medical Sciences between February – September 2018. In addition, age-matched healthy controls with no inflammatory rheumatic diseases were included. All patients were visited by a rheumatologist, an ophthalmologist and other specialists if needed. Demographic data of patients and healthy controls were obtained by direct interview. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences and performed according to the Helsinki humanity research declaration (2008) and written informed consent was obtained from all subjects before inclusion in the study. During the study, all the personal information was kept confidential and other ethical and humanitarian considerations were performed accordingly.

2.2. Clinical and biochemical measurements

At baseline, all participants were examined by a rheumatologist and BD activity was evaluated by Behcet's Disease Current Activity Form (BDCAF), Iranian Behcet's Disease Dynamic Activity Measure (IBDDAM) and Total Inflammatory Activity Index (TIAI) [34–36]. IBDDAM measure BD activity in all organs except eyes and TIAI measures BD activity in eyes [35]. Patients with BDCAF score ≥ 1 were considered as being in the disease's active period [36]. Then, 5 mL of venous blood samples were collected after 12 -h overnight fasting. The serum samples were separated from whole blood and were kept at −70 °C until biochemical analysis. Serum IL-9 (BioLegend Inc., USA) levels were measured by ELISA according to the manufacturer's recommendations, using an ELISA plate reader (Model stat fax 2100, Awareness, Ramsey, MN).

2.3. Statistical analysis

Statistical analysis was performed using SPSS software version 16.0 (SPSS, Inc., Chicago, USA). Normality of variables distribution was evaluated using the Kolmogorov-Smirnov test. Categorical and normally distributed quantitative variables were displayed as numbers (percentages) and means ± SD, respectively. Variables not normally distributed were presented using as median (Min–Max). Between groups comparisons were made by chi-squared test, and independent-sample t test, as appropriate. Correlations between variables were analyzed by Spearman rank correlation coefficient. $P < 0.05$ was considered statistically significant.

3. Results

In this study we analyzed IL-9 serum levels in 32 BD patients and 56 healthy controls. The mean ± SD age of patients and healthy controls was 39.06 ± 9.86 and 38.46 ± 8.03, respectively. No significant difference was observed in age between BD patients and controls ($P = 0.758$). 41% (n = 13) of the BD patients and 66% (n = 37) of controls were males ($P = 0.020$). As indicated in Table 1, the most common clinical symptoms in BD patients were oral aphthous ulcers, ocular involvement, and genital ulcers, respectively. Furthermore, there was no significant difference in serum IL-9 levels between BD patients (47.12 ± 7.34 mg/dL) and healthy controls (48.61 ± 7.76 mg/dL) ($P = 0.381$).

Table 2 shows correlation between serum IL-9 levels and clinical characteristics of BD patients. As indicated in Table 2, no significant correlations were observed between serum IL-9 levels and BD clinical characteristics ($P > 0.05$). In addition, according to Figs. 1 and 2, there were no significant correlations between serum IL-9 levels with disease severity ($P > 0.05$). Based on BDCAF score ≥ 1 [36], the majority of our patients (n = 29) were in the disease's active period and only 3 patients had inactive disease. No significant correlation was found between serum IL-9 levels with disease activity classification according to BDCAF (r = 0.107, $P = 0.558$).

Table 1
Demographic, clinical and biochemical characteristics of BD patients (n = 32).

Characteristics	BD patients (n = 32)
Age (years)	39.06 ± 9.86
Gender (male/female)	13/19
Oral aphthous ulcer (%)	30 (93.8)
Ocular involvement (%)	25 (78.1)
Severe ocular involvement (%)	20 (62.5)
Genital ulcer (%)	16 (50)
Pseudofolliculitis (%)	10 (31.2)
Positive Pathergy test (%)	8 (25)
Arthritis (%)	7 (21.9)
Erythema nodosum (%)	2 (6.2)
Phlebitis (%)	3 (9.4)
CNS involvement (%)	1 (3.1)
BDCAF	2 (0-4)
IBDDAM	1.3 (0–7)
TIAI	2 (0–22)
Serum IL-9 (mg/dL)	47.12 ± 7.34

BD, Behcet's Disease; GI, Gastrointestinal; CNS, Central Nervous System; BDCAF, Behcet's Disease Current Activity Form; IBDDAM, Iranian Behcet's Disease Dynamic Activity Measure; TIAI, Total Inflammatory Activity Index. Data were presented as numbers (percentages), median (Min–Max) or means ± SD, as appropriate.

Table 2
Correlation between serum IL-9 levels and clinical characteristics of BD patients (n = 32).

Clinical characteristics	Serum IL-9 (mg/dL)	
	r	P*
Oral aphthous ulcer	−0.245	0.184
Genital ulcer	0.054	0.772
Arthritis	0.228	0.218
Erythema nodosum	−0.206	0.267
Pseudofolliculitis	0.031	0.869
Phlebitis	0.122	0.513
CNS involvement	0.031	0.870
Positive Pathergy test	−0.036	0.866
Ocular involvement	−0.104	0.585
Severe eye involvement	−0.066	0.718

BD, Behcet's Disease; CNS, Central Nervous System.
* Spearman rank correlation coefficient.

4. Discussion

BD is a complex chronic autoinflammatory disorder in which abnormalities of neutrophils, endothelial cells, or both, have been indicated to be responsible for various clinical features of BD [37]. Furthermore, activation of circulating B and T lymphocytes occurs, and these immunoactive cells infiltrate into the affected regions followed by a second phase of neutrophil chemotaxis [37]. Considering this immunological activity in BD, pro-inflammatory cytokines and mediators may have an effect in the course of the disease. Cytokines are known to be important in different immune-inflammatory responses and may have a role in BD prognosis [37]. To clarify the etiopathogenesis of BD, several investigations have been performed on various serum cytokines. In recent years, IL-9 has gained interest since its expression is identified in multiple Th cell subsets including Th2, Th9, Th17, regulatory T cells (Treg) and natural killer (NK)/T cells [11]. IL-9 is a member of the gamma-chain family of cytokines, first described as a member of a growing number of cytokines that have key roles in the development, proliferation, survival, and differentiation of multiple cell lineages of both the innate and adaptive immune systems [38]. Recent studies have demonstrated that IL-9 or Th9 cells are involved in autoimmune inflammation and development of immune disorders [39].

To the best of our knowledge, this is the first study to evaluate serum IL-9 levels in patients with BD compared to healthy subjects and to assess whether there is an association between serum IL-9 levels and disease characteristics in BD patients. Based on present study, there was no significant difference in serum IL-9 level between BD patients and healthy controls. Furthermore, there were no significant correlations between serum IL-9 levels with disease severity as well as clinical characteristics. Recently, there are limited studies that have evaluated

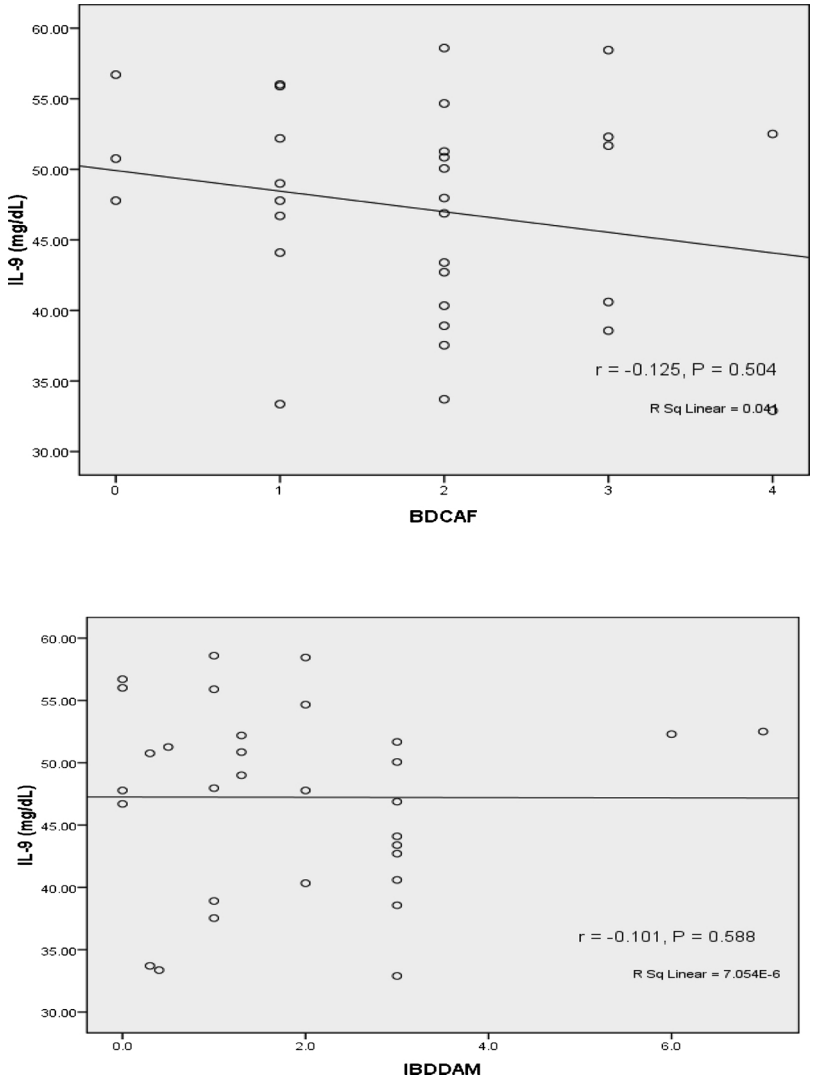

Fig. 1. Correlation between serum IL-9 levels and disease activity in BD patients (n = 32).

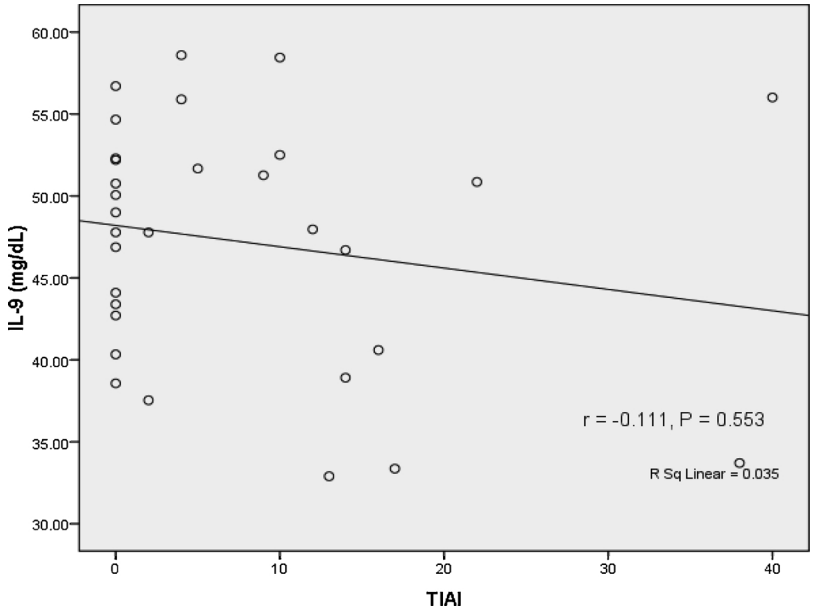

Fig. 2. Correlation between serum IL-9 levels and TIAI in BD patients (n = 32).

serum IL-9 in the context of rheumatic disorders. Our study was consistent with the only report in BD which indicated that the expression of IL-9 in PBMCs was not significantly different between active BD patients and normal controls as well as inactive patients [40]. However, PBMCs obtained from active, untreated systemic Granulomatosis with polyangiitis (GPA) patients presented skewed Th9 and Th17 responses, showing a GPA-specific mechanism of immune polarization [41]. In contrast with our study, in patients with giant cell arteritis (GCA) [29], IL-9 overexpression and Th9 polarization were reported in arteries with transmural inflammation and small-vessel vasculitis. The tissue expression of IL-9 was correlated with the intensity of the systemic inflammatory response, and IL-9R was also overexpressed in the GCA arteries [29]. Our results were also different from Pan et al. [30] study who showed that serum IL-9 levels and peripheral blood Th9 cells were significantly higher in patients with Takayasu's arteritis (TAK) compared to healthy controls and the levels of IL-9 had a significant positive correlation with ESR in these patients [30]. Furthermore, our study was not consistent with Ciccia et al. [42] who demonstrated for the first time that IL-9 is strongly over-expressed in the gut of psoriatic arthritis (PsA) patients, and that Th9 lymphocytes were the major source of IL-9 in PsA, highlighting the role of adaptive branch of immunity in the production of IL-9. They also indicated increased expression of IL-9 and IL-9R in PsA synovial tissues [42]. Moreover, Ciccia et al. [13] found that IL-9 and IL-9R were overexpressed in the synovial tissues of RA patients, which was correlated with the degree of synovial inflammatory infiltrate and ectopic lymphoid follicle organization. IL-9 levels are also elevated significantly in the synovial fluid of RA patients compared to osteoarthritis (OA) and IL-9 promotes proliferation and survival of synovial fluid $CD3^{(+)}$ T cells of RA patients [43]. In another study, Peng et al. [40] indicated that IL-9 mRNA levels in PBMCs were significantly elevated in patients with active Vogt-Koyanagi-Harada (VKH) disease, a systemic autoimmune disease, compared to those in patients with inactive VKH disease and normal controls. They concluded that IL-9 was involved in the pathogenesis of VKH disease, and that IL-9 might also enhance the inflammatory response by increasing the secretion of IL-17, an established proinflammatory cytokine in VKH disease [39]. This discrepancy among studies may be due to the differences in study populations, disease duration, disease activity and IL-9 status, type, dosage and duration of medical therapies, as well as sensitivity of the assays applied and sample size. IL-9 has been shown to be a particularly complex cytokine with two apparently opposing pro-inflammatory and anti-inflammatory effects. Whether IL-9 is a pathogenic or protective cytokine is still unclear with respect to immune responses. Further studies are needed to clarify the interactions between IL-9 and the immune system and how these interactions may dictate the inflammatory effects (pro or anti) of IL-9. Moreover, it is necessary to evaluate the longitudinal changes of serum IL-9 levels in patients with BD and to assess the association with disease activity.

The limitations of the present study included the relatively small sample size and that there was no a disease control group such as vasculitis. In addition, the cross-sectional nature of the present study could not reflect serum IL-9 changes during the treatment course. A longitudinal analysis will be more useful for evaluation of serum IL-9 variations in order to consider it as an active marker for BD. The strength of present study was that we had a control group and compared mean serum IL-9 levels between patients with BD and normal subjects.

5. Conclusion

In conclusion, our study revealed no significant difference in serum IL-9 between BD patients and healthy controls as well as no significant correlation between serum IL-9 with clinical characteristics and disease severity according to BDCAF, IBDDAM, and TIAI. Further studies are certainly needed, but on a wider cohort of BD patients to identify IL-9 involvement in BD pathogenesis. In addition, a disease control group is required in order to understand the actual role of IL-9 in BD.

Conflicts of interest

The authors declared that they have no conflicts of interests.

Funding

The authors wish to thank the Connective Tissue Diseases Research Center of Tabriz University of Medical Sciences, Tabriz, Iran for financial support.

Acknowledgments

The results of this article are derived from the MD thesis of Masoud Nouri-Vaskeh registered in the Tabriz University of Medical Sciences,

Tabriz, Iran. The authors wish to thank all the subjects for their participation in this research.

References

[1] J.R. Nair, R.J. Moots, Behcet's disease, Clin. Med. 17 (1) (2017) 71–77.
[2] R. Deniz, A. Tulunay-Virlan, F. Ture Ozdemir, A.U. Unal, G. Ozen, F. Alibaz-Oner, et al., Th17-Inducing conditions lead to in vitro activation of both Th17 and Th1 responses in Behcet's disease, Immunol. Invest. 46 (5) (2017) 518–525.
[3] K. Hamzaoui, Th17 cells in Behcet's disease: a new immunoregulatory axis, Clin. Exp. Rheumatol. 29 (Suppl 67) (2011) S71–6.
[4] S. Demirelli, H. Degirmenci, S. Inci, A. Arisoy, Cardiac manifestations in Behcet's disease, Intractable Rare Dis. Res. 4 (2) (2015) 70–75.
[5] F.N. Yalçindağ, A. Yalçindağ, O. Çağlayan, Ö. Özdemir, Serum haptoglobin levels in ocular Behçet disease and acute phase proteins in the course of Behçet disease, Eur. J. Ophthalmol. 18 (2008) 787–791.
[6] A. Sadeghi, F. Davatchi, F. Shahram, A. Karimimoghadam, M. Alikhani, A. Pezeshgi, et al., Serum profiles of cytokines in Behcet's Disease, J. Clin. Med. 6 (5) (2017) 49–53.
[7] O.M. Lucherini, G. Lopalco, L. Cantarini, G. Emmi, A. Lopalco, V. Venerito, et al., Critical regulation of Th17 cell differentiation by serum amyloid-a signalling in Behcet's disease, Immunol. Lett. 201 (2018) 38–44.
[8] Y. Deng, Z. Wang, C. Chang, L. Lu, C.S. Lau, Q. Lu, Th9 cells and IL-9 in autoimmune disorders: pathogenesis and therapeutic potentials, Hum. Immunol. 78 (2) (2017) 120–128.
[9] G. Lopalco, O.M. Lucherini, A. Lopalco, V. Venerito, C. Fabiani, B. Frediani, et al., Cytokine signatures in mucocutaneous and ocular Behçet's disease, Front. Immunol. 27 (8) (2017) 200–209.
[10] G. Lopalco, O.M. Lucherini, A. Vitale, R. Talarico, A. Lopalco, M. Galeazzi, et al., Putative role of serum amyloid-a and proinflammatory cytokines as biomarkers for Behcet's disease, Medicine (Baltimore) 94 (42) (2015) e1858–64.
[11] F. Ciccia, G. Guggino, A. Ferrante, P. Cipriani, R. Giacomelli, G. Triolo, Interleukin-9 and T helper type 9 cells in rheumatic diseases, Clin. Exp. Immunol. 185 (2) (2016) 125–132.
[12] H. Li, A. Rostami, IL-9: basic biology, signaling pathways in CD4+ T cells and implications for autoimmunity, J. Neuroimmune Pharmacol. 5 (2) (2010) 198–209.
[13] F. Ciccia, G. Guggino, A. Rizzo, A. Manzo, B. Vitolo, M.P. La Manna, et al., Potential involvement of IL-9 and Th9 cells in the pathogenesis of rheumatoid arthritis, Rheumatology (Oxford) 54 (12) (2015) 2264–2272.
[14] T.P. Singh, M.P. Schon, K. Wallbrecht, A. Gruber-Wackernagel, X.J. Wang, P. Wolf, Involvement of IL-9 in Th17-associated inflammation and angiogenesis of psoriasis, PLoS One 8 (1) (2013) e51752–62.
[15] N. Sismanopoulos, D.A. Delivanis, K.D. Alysandratos, A. Angelidou, M. Vasiadi, A. Therianou, T.C. Theoharides, IL-9 induces VEGF secretion from human mast cells and IL-9/IL-9 receptor genes are overexpressed in atopic dermatitis, PLoS One 7 (3) (2012) e33271–5.
[16] G. Ciprandi, M. De Amici, V. Giunta, A. Marseglia, G. Marseglia, Serum interleukin-9 levels are associated with clinical severity in children with atopic dermatitis, Pediatr. Dermatol. 30 (2) (2013) 222–225.
[17] L. Ma, H.B. Xue, X.H. Guan, C.M. Shu, J.H. Zhang, J. Yu, Possible pathogenic role of T helper type 9 cells and interleukin (IL)-9 in atopic dermatitis, Clin. Exp. Immunol. 175 (1) (2014) 25–31.
[18] H. Ouyang, Y. Shi, Z. Liu, S. Feng, L. Li, N. Su, et al., Increased interleukin 9 and CD4+IL-9+ T cells in patients with systemic lupus erythematosus, Mol. Med. Rep. 7 (3) (2013) 1031–1037.
[19] C.C. Luk, L.S. Tam, B.C. Kwan, P.C. Wong, T.K. Ma, K.M. Chow, F.M. Lai, P.K. Li, C.C. Szeto, Intrarenal and urinary Th9 and Th22 cytokine gene expression in lupus nephritis, J. Rheumatol. 42 (7) (2015) 1150–1155.
[20] K. Yanaba, A. Yoshizaki, Y. Asano, T. Kadono, S. Sato, Serum interleukin 9 levels are increased in patients with systemic sclerosis: association with lower frequency and severity of pulmonary fibrosis, J. Rheumatol. 38 (10) (2011) 2193–2197.
[21] M. Ryba-Stanislawowska, P. Werner, A. Brandt, M. Mysliwiec, J. Mysliwska, Th9 and Th22 immune response in young patients with type 1 diabetes, Immunol. Res. 64 (3) (2015) 730–735.
[22] G. Ruocco, S. Rossi, C. Motta, G. Macchiarulo, F. Barbieri, M. De Bardi, et al., T helper 9 cells induced by plasmacytoid dendritic cells regulate interleukin-17 in multiple sclerosis, Clin. Sci. 129 (4) (2015) 291–303.
[23] J. Yang, Q. Li, X. Yang, M. Li, Interleukin-9 is associated with elevated anti-double-Stranded DNA antibodies in Lupus-Prone Mice, Mol. Med. 21 (2015) 364–370.
[24] H. Li, B. Nourbakhsh, B. Ciric, G.X. Zhang, A. Rostami, Neutralization of IL-9 ameliorates experimental autoimmune encephalomyelitis by decreasing the effector T cell population, J. Immunol. 185 (7) (2010) 4095–4100.
[25] A. Jager, V. Dardalhon, R.A. Sobel, E. Bettelli, V.K. Kuchroo, Th1, Th17, and Th9 effector cells induce experimental autoimmune encephalomyelitis with different pathological phenotypes, J. Immunol. 183 (11) (2009) 7169–7177.
[26] Y. Yang, L. Du, M. Sun, A. Kijlstra, P. Yang, IFN-beta inhibits the increased expression of IL-9 during experimental autoimmune uveoretinitis, PLoS One 7 (10) (2012) e48566–71.
[27] X. Yao, Q. Kong, X. Xie, J. Wang, N. Li, Y. Liu, et al., Neutralization of interleukin-9 ameliorates symptoms of experimental autoimmune myasthenia gravis in rats by decreasing effector T cells and altering humoral responses, Immunology 143 (3) (2014) 396–405.
[28] J.C. Jennette, R.J. Falk, P.A. Bacon, N. Basu, M.C. Cid, F. Ferrario, Revised international chapel hill consensus conference nomenclature of vasculitides, Arthritis Rheum. 65 (1) (2012) 1–11.
[29] F. Ciccia, A. Rizzo, G. Guggino, A. Cavazza, R. Alessandro, R. Maugeri, et al., Difference in the expression of IL-9 and IL-17 correlates with different histological pattern of vascular wall injury in giant cell arteritis, Rheumatology (Oxford) 54 (9) (2015) 1596–1604.
[30] L. Pan, J. Du, N. Gao, H. liao, J. wan, W. Ci, C. Yang, T. Wang, IL-9-producing Th9 cells may participate in pathogenesis of Takayasu's arteritis, Clin. Rheumatol. 35 (12) (2016) 3031–3036.
[31] International Team for the Revision of the International Criteria for Behcet's Disease (ITR-ICBD), The International Criteria for Behcet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria, J. Eur. Acad. Dermatol. Venereol. 28 (3) (2014) 338–347.
[32] F. Davatchi, Diagnosis/classification criteria for Behcet's disease, Pathol. Res. Int. 2012 (2012) 1–5.
[33] F. Davatchi, S. Assaad-Khalil, K.T. Calamia, J.E. Crook, B. Sadeghi-Abdollahi, M. Schirmer, et al., The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria, J. Eur. Acad. Dermatol. Venereol. 28 (3) (2014) 338–347.
[34] G. Lawton, B. Bhakta, M. Chamberlain, A. Tennant, The Behcet's disease activity index, Rheumatology 43 (1) (2004) 73–78.
[35] F. Davatchi, M. Akbarian, F. Shahram, M.E. Tebbi, C. Chams, H. Chams, Iran Behcet's disease dynamic activity measure. Abstracts of the XIIth European congress of rheumatology, Hung. Rheumatol. 32 (2019) 134 (abstract FP10–100).
[36] F. Shahram, A. Khabbazi, A. Nadji, N. Ziaie, A.T. Banihashemi, F. Davatchi, Comparison of existing disease activity indices in the follow-up of patients with Behcet's disease, Mod. Rheumatol. 19 (5) (2009) 536–541.
[37] Bainan Tong, Xiaoli Liu, Jun Xiao, Su Guanfang, Immunopathogenesis of Behcet's Disease, Front. Immunol. 10 (2019) 665–676.
[38] Y. Rochman, R. Spolski, W.J. Leonard, New insights into the regulation of T cells by gamma(c) family cytokines, Nat. Rev. Immunol. 9 (7) (2009) 480–490.
[39] H.F. Pan, R.X. Leng, X.P. Li, S.G. Zheng, D.Q. Ye, Targeting T-helper 9 cells and interleukin-9 in autoimmune diseases, Cytokine Growth Factor Rev. 24 (6) (2013) 515–522.
[40] Z. Peng, S. Jiang, M. Wu, X. Zhou, Q. Wang, Expression and role of interleukin-9 in Vogt-Koyanagi-Harada disease, Mol. Vis. 23 (2017) 538–547.
[41] A. Millet, K.R. Martin, F. Bonnefoy, P. Saas, J. Mocek, M. Alkan, et al., Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis, J. Clin. Invest. 125 (11) (2015) 4107–4121.
[42] F. Ciccia, G. Guggino, A. Ferrante, S. Raimondo, R. Bignone, V. Rodolico, et al., IL-9 over-expression and Th9 polarization characterize the inflamed gut, the synovial tissue and the peripheral blood of patients with psoriatic arthritis, . 68 (8) (2016) 1922–1931.
[43] S. Kundu-Raychaudhuri, C. Abria, Raychaudhuri SP. IL-9, a local growth factor for synovial T cells in inflammatory arthritis, Cytokine 79 (2016) 45–51.