

Report

A proliferation-inducing ligand in atopic dermatitis and vitiligo

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Funding: None.

Conflicts of interest: None.

doi: 10.1111/ijd.12176

Abstract

Background A proliferation-inducing ligand (APRIL) is a tumor necrosis factor (TNF) superfamily member ligand that stimulates B cells *in vitro* and *in vivo*. It also plays an important role in T cell activation and survival.

Objectives This study was conducted to evaluate serum levels of APRIL in patients with atopic dermatitis (AD) and vitiligo and their correlation with disease activity.

Methods A total of 100 subjects were included; these comprised 40 AD patients, 40 vitiligo patients, and 20 control subjects. Serum APRIL levels were measured and their relationships with the severity of AD and activity of vitiligo evaluated according to scores on the SCORAD (SCORing of Atopic Dermatitis) and VIDA (Vitiligo Disease Activity) indices, respectively.

Results The serum level of APRIL was significantly higher in AD patients than in the control group. Serum APRIL in patients with severe AD showed a statistically significant difference with serum APRIL in patients with either mild or moderate AD. Serum APRIL was significantly higher in vitiligo patients than in the control group. Differences in serum APRIL among patients with different VIDA scores were significant only between patients with VIDA scores of +1 and +4. Statistically significant positive correlations emerged between serum APRIL and activity of AD ($r = 0.939$) and vitiligo ($r = 0.740$).

Conclusions APRIL may play a role in the pathogenesis of AD and vitiligo and could be used as an objective marker for the assessment of AD severity and vitiligo activity. Further studies are required to clarify the precise mechanism of APRIL in the pathogenesis of AD and vitiligo and to test the possible use of APRIL inhibitors as novel modalities of therapy.

Introduction

A proliferation-inducing ligand (APRIL) is a tumor necrosis factor (TNF) superfamily member ligand that is produced by several cell types, including monocytes, macrophages, neutrophils, dendritic cells, and T lymphocytes. APRIL acts mainly on two receptors, the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), and the B cell maturation antigen (BCMA).¹ APRIL can attach to the cell surface as a natural fusion protein with TNF-like weak inducer of apoptosis (TWEAK). APRIL costimulates B cells *in vitro* and *in vivo*. In addition, it plays an important role in T cell activation and survival. APRIL also activates immunoglobulin G (IgG), IgA, and IgE isotype switching in B cells, independently of the CD40–D40L pathway, with the help of interleukin-4 (IL-4).² APRIL significantly enhances B cell antigen presentation to

T cells. This effect is mediated via BCMA. Expression of APRIL by many of the immune cells occurs in response to several cytokines such as interferon- α (IFN- α), IFN- γ , and CD40 ligand.³ In humans, increased serum levels of APRIL have been described in a number of autoimmune diseases, such as rheumatoid arthritis,⁴ systemic lupus erythematosus,⁵ and multiple sclerosis,⁶ and are often correlated with disease progression.⁷

Atopic dermatitis (AD) is a chronic, highly pruritic inflammatory skin disease characterized by the preferential infiltration of activated T cells, monocytes/macrophages, and eosinophils. It is well established that T cells contribute to the pathogenesis of AD.⁸ The T helper (Th) 2 cells play a key role in the pathogenesis of AD, whereas Th1-type cytokines, such as IFN- γ and IL-12, are predominantly expressed in chronic AD, and Th2 cytokines, such as IL-4, IL-5, and IL-13, increase IgE synthesis and peripheral blood eosinophils.⁹

Vitiligo is an acquired idiopathic hypomelanotic disorder caused by the loss of cutaneous melanocytes. Its etiology is still obscure. Autoimmunity is suggested to play a role in the development of vitiligo. Autoantibodies and autoreactive T lymphocytes that target pigment cells are detected in vitiligo patients.⁹ Strong evidence supports the autoimmune theory, in which B cell autoantibody production and autoreactive T cell cytotoxicity are involved in the pathogenesis of vitiligo.¹⁰

A literature review revealed controversy about serum APRIL levels in AD.^{11,12} By contrast, no reports of serum APRIL levels in vitiligo were found. Therefore, this study aimed to evaluate serum levels of APRIL in patients with AD and vitiligo, respectively, and to establish correlations with disease activity.

Materials and methods

The present study was conducted in a cohort of 100 subjects selected from the Outpatient Clinic in the Department of Dermatology and Venereology, Tanta University Hospital. Subjects were classified into 40 patients with AD, 40 patients with active vitiligo, and 20 healthy subjects who served as a control group. The study protocol and consent form were approved by the local ethics committee. Written informed consent was obtained from all adult patients and the parents of child participants.

The diagnosis of AD was made according to the criteria of Hanifin and Rajka.¹³ The severity of disease was assessed using the SCORing of Atopic Dermatitis Index (SCORAD).¹⁴ The SCORAD requires information on the extent of the affected body area, the intensity of six clinical signs (erythema, edema/papules, excoriation, oozing/crusts, lichenification, and dryness), and subjective symptoms (pruritus and loss of sleep during the previous three days). The SCORAD index (range: 0–103) is calculated as: $A/5 + 7B/2 + C$, where A is the total area with a maximum of 100%, B is the intensity score with a maximum of 18, and C is the subjective symptom score with a maximum of 20. Thus the maximum score obtainable is 103. The SCORAD index is used to classify disease into mild (SCORAD: < 25), moderate (SCORAD: 25–49), and severe (SCORAD: $\geq$ 50) presentations. The severity of AD in patients in this study was mild in 30% of patients ($n = 12$), moderate in 35% ($n = 14$) and severe in 35% ($n = 14$). Twelve (30%) AD patients had a history of other atopic manifestations such as asthma and allergic rhinitis.

Vitiligo patients were diagnosed according to their clinical presentation. All patients encountered in this study presented generalized vitiligo (non-segmental type). Vitiligo was classified according to clinical type as vulgaris (24 patients, 60%), acrofacial (six patients, 15%), and mixed (10 patients, 25%) vitiligo. The activity of disease was assessed using the Vitiligo Disease Activity (VIDA) score,¹⁵ which uses a 6-point scale ranging from –1 to +4 based on duration of disease and the

expansion of existing lesions or appearance of new lesions. Active lesions that appeared in $\leq$ 6 weeks warranted a VIDA score of +4; lesions that emerged over 6 weeks to 3 months gave a score of +3; lesions that emerged within 3–6 months gave a score of +2, and lesions that developed over a period of 6–12 months gave a score of +1. Vitiligo that had remained stable for $\geq$ 1 year was scored as +0; stable vitiligo with spontaneous repigmentation was scored as –1. A low VIDA score indicates less activity. Vitiligo patients classified according to VIDA scores included 12 patients (30%) with a VIDA score of +1, eight patients (20%) with a VIDA score of +2, 10 patients (25%) with a VIDA score of +3, and 10 patients (25%) with a VIDA score of +4. Exclusion criteria included the presence of any systemic autoimmune disease, other dermatological disease, pregnancy, lactation, and receipt of systemic or topical treatment or phototherapy within the six weeks prior to the study's start.

Specimen sample collection and preparation for analysis

Fresh venous blood samples of 3 ml were collected in blank tubes without anticoagulant and centrifuged. Serum was removed using a sterile pipette and stored at -20°C until it was subjected to enzyme-linked immunosorbent assay (ELISA) for the determination of serum APRIL. We used the human APRIL ELISA kit (Bender Med Systems GmbH, Vienna, Austria) according to the manufacturer's instructions.¹¹ A standard curve was created by plotting the mean absorbance for each standard concentration on the ordinate against the APRIL concentration on the abscissa. A best-fit curve was drawn through the points of the graph. The concentration of circulating APRIL in each sample was determined. The concentration read from the standard curve was multiplied by the dilution factor ($\times 2$).

Statistical analysis

Statistical analysis was conducted using SPSS Version 17 (SPSS, Inc., Chicago, IL, USA). Comparisons between two groups were performed using *t*-tests. The linear correlation coefficient was used to detect correlations between two quantitative variables in one group. Analysis of variance (ANOVA) was used to compare quantitative data within the same group.

Results

Clinical assessment

Demographic characteristics and the disease profile of the study cohort are described in Table 1.

Laboratory results

Mean serum levels of APRIL in AD and vitiligo patients were significantly higher than in the control group ($P < 0.001$). The difference between mean serum levels of APRIL in AD patients and vitiligo patients was not

Table 1 Demographic data for control subjects and atopic dermatitis (AD) and vitiligo patients

	Control group	AD patients	Vitiligo patients
Subjects, <i>n</i>	20	40	40
Age, years, mean $\pm$ SD	18.4 $\pm$ 12.0	14.5 $\pm$ 6.4	25.4 $\pm$ 14.3
Gender, M/F, <i>n</i>	10/10	22/18	25/15
Duration of disease, months, mean $\pm$ SD		28.5 $\pm$ 38.8	34.6 $\pm$ 29.3

ANOVA, analysis of variance; SD, standard deviation; M, male; F, female.

Table 2 Serum APRIL levels in control subjects and atopic dermatitis (AD) and vitiligo patients

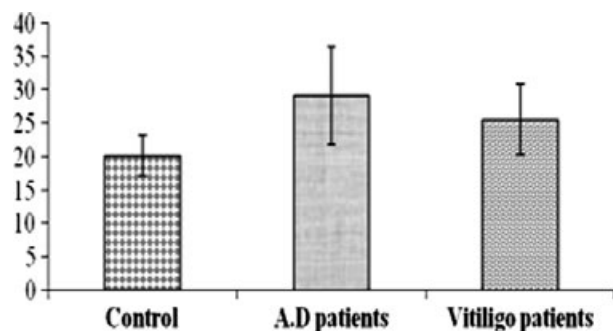
	APRIL level, ng/ml		ANOVA	
	Range	Mean $\pm$ SD	F-value	P-value
Control subjects	14–25	20.2 $\pm$ 3.1	13.3	<0.001 ^a
AD patients	18–45	29.2 $\pm$ 7.4		
Vitiligo patients	18–37	25.6 $\pm$ 5.3		

Tukey's test

Control vs. AD group	<0.001 ^a
Control vs. vitiligo group	0.009 ^a
AD vs. vitiligo group	0.108

^aThis difference is significant.

ANOVA, analysis of variance; SD, standard deviation.

**Figure 1** Comparison of serum APRIL levels in control subjects and atopic dermatitis (AD) and vitiligo patients. SD, standard deviation. Bars represent 95% confidence intervals

statistically significant (Table 2, Fig. 1). Mean serum APRIL was higher in severe AD than in either mild or moderate AD; this difference was statistically significant ($P < 0.001$). There was no significant difference in serum APRIL between mild and moderate AD ($P = 0.076$)

Table 3 Relationship between serum APRIL in atopic dermatitis patients and severity of disease according to SCORAD score

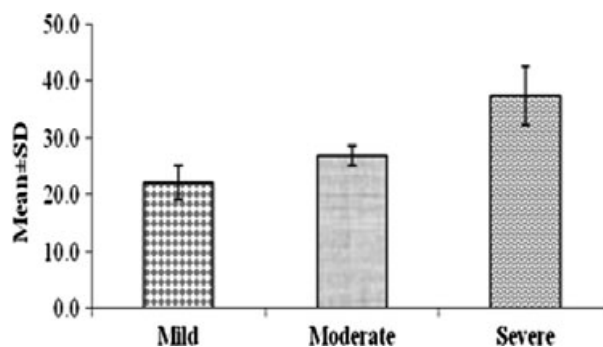
SCORAD	APRIL level, ng/ml		ANOVA	
	Range	Mean $\pm$ SD	F-value	P-value
Mild < 25	18–25	22.2 $\pm$ 2.9	31.3	<0.001 ^a
Moderate < 50	25–30	26.9 $\pm$ 1.7		
Severe $\geq$ 50	32–45	37.4 $\pm$ 5.1		

Tukey's test

Mild vs. moderate	0.076
Mild vs. severe	<0.001 ^a
Moderate vs. severe	<0.001 ^a

^aThis difference is significant.

ANOVA, analysis of variance; SD, standard deviation.

**Figure 2** Correlation of serum APRIL in atopic dermatitis (AD) patients and severity of AD according to SCORAD score. SD, standard deviation. Bars represent 95% confidence intervals

(Table 3, Fig. 2). By contrast, mean serum APRIL in vitiligo patients with a VIDA score of +4 was higher than in vitiligo patients with lower VIDA scores ($P = 0.004$), but the only significant difference occurred between vitiligo patients with VIDA scores of +1 and +4, respectively ($P = 0.002$) (Table 4, Fig. 3). Mean serum APRIL was higher in mixed vitiligo than in the other types of vitiligo, although the difference did not achieve significance (Table 5). There were statistically significant positive correlations ($P < 0.001$) between serum APRIL and activity of AD ($r = 0.939$) and vitiligo ($r = 0.740$) according to SCORAD and VIDA scores, respectively (Figs 4 and 5).

Discussion

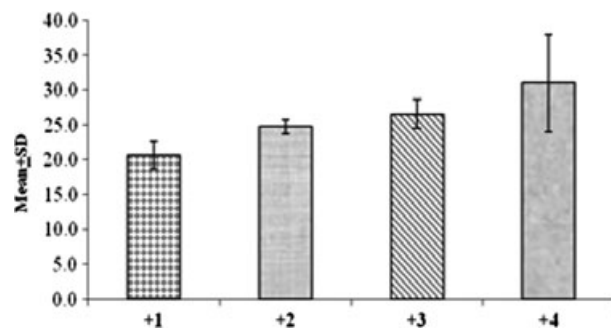
The role of B cells in allergy is indisputable, and their contribution beyond IgE production has recently begun to be appreciated. However, the factors influencing B cell

Table 4 Relationship between serum APRIL in vitiligo patients and severity of disease according to VIDA score

VIDA score	APRIL level, ng/ml		ANOVA		
	Range	Mean $\pm$ SD	F-value	P-value	
+1	18–23	20.7 $\pm$ 1.9	6.9	0.004 ^a	
+2	24–26	24.8 $\pm$ 0.9			
+3	24–29	26.6 $\pm$ 2.1			
+4	23–37	31.0 $\pm$ 6.9			
Tukey's test					
1 vs. 2	1 vs. 3	1 vs. 4	2 vs.3	2 vs.4	3 vs.4
0.377	0.087	0.002 ^a	0.887	0.109	0.299

^aThis difference is significant.

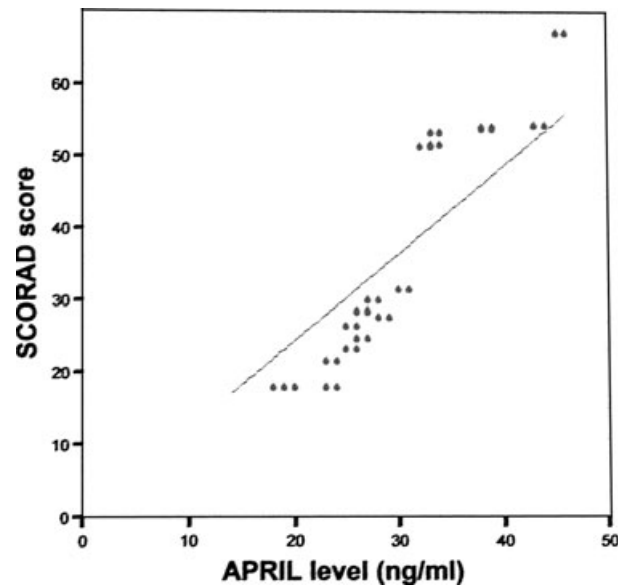
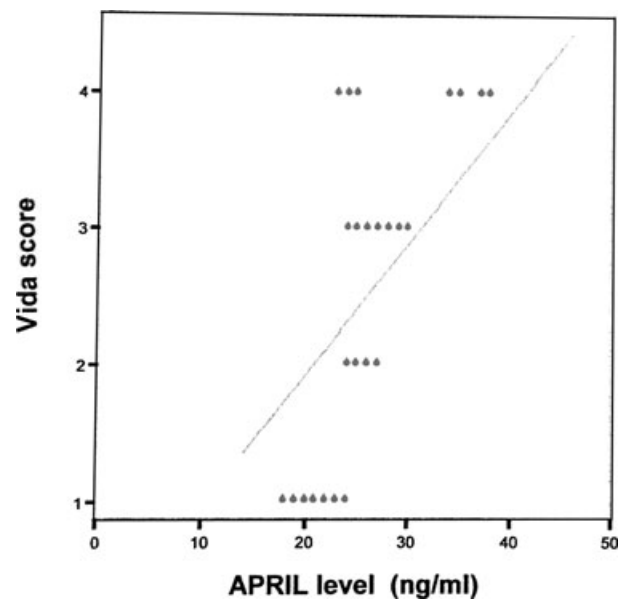
ANOVA, analysis of variance; SD, standard deviation.

**Figure 3** Correlation between serum APRIL level in vitiligo patients and activity of vitiligo according to VIDA score. SD, standard deviation. Bars represent 95% confidence intervals**Table 5** Comparison between mean levels of serum APRIL in different clinical types of vitiligo

Vitiligo type	APRIL level, ng/ml		ANOVA	
	Range	Mean $\pm$ SD	F-value	P-value
Vulgaris	19–37	25.4 $\pm$ 5.4	1.009	0.385
Mixed	23–37	27.8 $\pm$ 5.5		
Acrofacial	18–25	22.3 $\pm$ 3.8		

ANOVA, analysis of variance; SD, standard deviation.

activation and homeostasis in allergic diseases, in both systemic and target tissue environments, need to be characterized.¹⁶ In this study, serum APRIL level was significantly higher in AD patients and was positively correlated with disease severity as detected by SCORAD score. This suggests a possible role for APRIL in the pathogenesis of AD. Matsushita *et al.*¹¹ reported that serum levels of

**Figure 4** Correlation between serum APRIL and SCORAD score in atopic dermatitis patients ($r = 0.939$). SD, standard deviation**Figure 5** Correlation between serum APRIL and VIDA score in vitiligo patients ($r = 0.740$). SD, standard deviation

APRIL were significantly elevated in patients with AD and that the difference between the higher values in severe AD and those in moderate and mild AD was statistically significant. These authors also reported that elevated serum APRIL in AD patients was significantly

associated with elevated serum IgE and eosinophilia.¹¹ This would explain the association of a higher level of serum APRIL and severe AD. In the same study, the authors revealed a significant decrease in serum APRIL after treatment and concluded that serum APRIL could be considered a prognostic marker in AD.¹¹ By contrast, Chen *et al.*¹² reported that circulating levels of APRIL were not elevated in AD patients and did not correlate with AD severity. It is not clear why serum APRIL was not found to be elevated in their patient cohort. However, possible explanations may refer to disease subtypes and different patient selection criteria. Chen *et al.* also found that 74% of their AD patients suffered from asthma or rhinitis and there is some probability that medication for asthma and rhinitis may impose a negative effect on serum APRIL.¹² It has been suggested that keratinocytes in skin, in addition to performing a barrier function, can also secrete numerous cytokines, chemokines and some of the growth factors in an autocrine manner regulating barrier homeostasis, and this ability of keratinocytes has been shown to be dysregulated in AD lesional skin.¹⁷

From another point of view, decreased APRIL expression in AD skin can be explained by the fact that APRIL binding to TACI delivers a negative signal to B cells. As APRIL does not bind to the B cell activating factor of the TNF family (BAFF) receptor, it does not deliver a BAFF receptor-mediated positive signal to B cells. Therefore, the decreased expression of APRIL in eczema skin may contribute to a reduced negative regulatory input to B cells, which is more pronounced in the initiating acute stage of AD, resulting in the dysregulation of overactivated B cells in lesional skin.¹²

APRIL was found to be upregulated in response to a number of different pathogenic stimuli, which suggests that it may have a role in early innate immunity.¹⁸ The release of APRIL by dendritic cells was shown to be mediated by signaling via the toll-like receptor which is expressed in AD in response to invading microbes.¹⁹ In AD, T lymphocytes differentiate towards a Th2 phenotype. A second exposure to the antigen causes cell reactivation and mast cell degradation, with the release of histamine and inflammatory cytokines such as IL-8 and IL-13. This cytokine milieu causes an influx of Th2 lymphocytes and eosinophils into the skin, with the production of Th2 cytokines such as IL-4, IL-5 and IL-13, which, in turn, stimulate eosinophils to release IL-25, enhancing the Th2 environment. During the acute phase, eosinophils produce IL-6, IL-1 β and transforming growth factor- β (TGF- β),²⁰ whereas mast cells and basophils express CD40 ligand and T cells release IFN- α and IFN- γ .²¹ The expression of APRIL occurs in response to several cytokines, such as IFN- α , IFN- γ and CD40 ligand

(CD40L).¹⁹ These cytokines, together with keratinocytes (expressing TLR), may be responsible for the increased serum APRIL in AD.

The role of APRIL in AD is still unclear, but it may be elucidated through its effect on B cells. APRIL is an essential molecule for the development, survival and proliferation of B cells. In the presence of IL-4, APRIL induces class switching of B lymphocytes to IgE production, which binds to high-affinity IgE receptors on tissue resident mast cells.²² APRIL is upregulated in activated T cells and thus during B cell–T cell interactions can synergize with CD40 to enhance antigen presentation by B cells. APRIL expression on B cells can be induced following CD40 stimulation, which raises the possibility that CD40 may also provide a feed-forward effect to B cell membrane, enhancing antigen presentation.²³ Excess APRIL may exacerbate AD skin lesions via T cell activation and survival.²⁴ The observation that anti-APRIL antibodies prevent T cell stimulation *in vitro* supports the proposed implication of APRIL in primary T cell activation.^{25,26}

With regard to vitiligo, our results revealed that serum APRIL was significantly increased in vitiligo patients and was positively correlated with disease activity as detected by VIDA score. This suggests that elevated serum APRIL may play a role in the pathogenesis of vitiligo. To the best of our knowledge, this is the first study to evaluate the role of serum APRIL in vitiligo. Although the theory of autoimmunity in vitiligo is the most accepted theory, the mechanism by which autoimmunity leads to the breakdown of self-tolerance in vitiligo remains obscure. As APRIL and BAFF bind to the same receptors on B cells, there is consequently a large overlap in their functions. Lin *et al.*²⁷ studied the possible role of BAFF in vitiligo autoimmunity. They postulate that the overexpression of BAFF may lead to the breakdown of self-tolerance and subsequently cause autoimmunity in vitiligo via the activation of B cells, CD4⁺ T cells and CD8⁺ T cells. Both B cell-produced antibodies and autoreactive T cell cytotoxicity have been demonstrated to be involved in the vitiligo-related disappearance of melanocytes.²⁸ Serum IgG antibodies from vitiligo patients, but not from healthy controls, have been shown to be capable of penetrating cultured melanocytes *in vitro* and triggering them to engage in apoptosis.²⁹ Furthermore, skin-homing melanocyte-specific cytotoxic T lymphocytes (CD8⁺ T cells) have been detected in the peripheral blood of vitiligo patients.³⁰

The expression of cell markers for cutaneous infiltrates at the periphery of vitiligo demonstrates that many of these T cells are skin-homing, activated cytotoxic T cells.³¹ Perilesional infiltrated T cells are mainly melanocyte-reactive CD8⁺ T cells, and these T cells destroy

skin melanocytes, causing depigmentation in vitiligo.³² A concurrent elevation in leucocyte inhibition factor released by activated T lymphocytes and circulating IgG suggests that a T cell-mediated B cell activation occurs.³³ This could explain the correlation between serum APRIL and VIDA score in vitiligo patients in this study. It could be suggested that the breakdown of the regulation of APRIL expression results in excessive APRIL production, impairing B cell tolerance and leading to autoantibody production with a subsequent role in autoimmune diseases.³⁴

As levels of APRIL in the plasma of patients with various autoimmune diseases are elevated, it is considered an important factor driving B cell autoantibody production. Studies of B cell function over the past two decades have implicated B cells in making multiple additional contributions to the pathogenesis of autoimmune disease. Excess APRIL induces changes in the B cell compartment, which, in turn, increases the number of effector T cells, possibly via the antigen-presenting cell function of B cells. Thus, APRIL-mediated autoimmune disorders may reflect a combination of pathogenic effects involving both B and T cells.³⁵ Data show that by adding anti-T cell receptor (TCR) stimulation, APRIL is able to regulate T cell activation by inducing IL-2 secretion and T cell division. APRIL activity has been observed on naïve as well as effector/memory T cells (both CD4⁺ and CD8⁺ subsets), indicating a wide impact of APRIL on T cell responses. Analysis of the signal transduced by APRIL showed that APRIL is able to deliver a complete costimulation signal into T cells. Thus, APRIL may play a role in the development of T cell responses, in addition to its role in B cell homeostasis.³⁶ As cellular and humoral immunity are involved in vitiligo autoimmunity, the breakdown of self-tolerance in both B cell and T cell compartments must take place in the pathogenesis of vitiligo. In this process, APRIL is considered to be one of the elements mediating the breakdown as it can regulate the activation of both B and T cells. Based on a collection of indirect evidence, it could be postulated that excessive expression of APRIL may result in the breakdown of self-tolerance and subsequent autoimmune reactions via the activation of B cells to produce autoantibodies in vitiligo. In addition, APRIL-activated B cells promote the activity of self-reactive CD4⁺ and CD8⁺ T cells in vitiligo.

Further studies with larger sample sizes are required to confirm our results, to clarify the possible involvement of APRIL in the pathogenesis of AD and vitiligo, to evaluate its expression in the skin of AD and vitiligo patients, and to test the possible use of APRIL inhibitors as novel modalities of therapy. Studying the correlations between different clinical features of AD, and IgE, eosinophilia and APRIL would broaden the scope of investigation. We

also suggest that APRIL in vitiligo should be further evaluated using a different scaling system.^{37,38}

Conclusions

Serum APRIL increases in patients with AD and vitiligo and could be highlighted as an objective marker for the assessment of severity of AD and activity of vitiligo.

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