

CORRELATIONS OF SERUM INTERLEUKIN-16, TOTAL IgE, EOSINOPHIL CATIONIC PROTEIN AND TOTAL EOSINOPHIL COUNTS WITH DISEASE ACTIVITY IN CHILDREN WITH ATOPIC DERMATITIS

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Several laboratory parameters have been investigated for assessing disease activity in children with atopic dermatitis (AD). Analyses of the correlation between these parameters and clinical severity can help to choose a convincing tool. This study compared the significance of serum interleukin-16 (IL-16), serum total immunoglobulin E (IgE), serum eosinophil cationic protein (ECP), and total eosinophil count (TEC) in reflecting AD severity to order to identify the most relevant objective tool for assessing AD activity and to assess the correlation between these laboratory parameters. The Severity Scoring of Atopic Dermatitis (SCORAD index) was used for the assessment of disease activity in 48 pediatric patients in the acute exacerbation phase and in the maintenance phase after improvement of clinical findings with conventional treatment for 8 weeks. Serum levels of total IgE, ECP, and IL-16 as well as TEC were measured on the same time points and compared with healthy non-atopic controls. The correlation between SCORAD and each laboratory parameter was tested for significance and compared. Serum levels of ECP and IL-16 of AD patients were significantly higher than those of controls. These serum parameters, except TEC, declined significantly after conventional treatment with clinical improvement. There was positive correlation with SCORAD for serum IgE ($r=0.317$, $p=0.028$), TEC ($r=0.434$, $p=0.002$), IL-16 ($r=0.321$, $p=0.026$) in the acute exacerbation phase and with SCORAD for serum IgE ($r=0.510$, $p<0.001$), TEC ($r=0.489$, $p<0.001$), serum ECP ($r=0.468$, $p=0.001$) in the maintenance phase. Serum levels of total IgE, IL-16, ECP, and TEC correlated with the SCORAD index in pediatric patients with atopic dermatitis. Thus, they can serve as serum markers for monitoring disease activity in childhood atopic dermatitis.

Atopic dermatitis (AD) is a chronic relapsing inflammatory pruritic skin disease that affects 10-15% of children (1). Its clinical pattern varies with age. Infants typically present with intensely pruritic and exudative erythematous papules and vesicles on the cheeks, forehead, or scalp. The childhood

phase, which typically occurs from two years of age to puberty, exhibits more lichenified papules and plaques representing the more chronic disease that involves the hands, feet, wrists, ankles, and antecubital and popliteal regions. In children with disease onset before the age of 2 years, 20% will

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have persistent manifestations into adulthood with predominant areas in the flexural folds, the face and neck, the upper arms and back, and the dorsa of the hands, feet, fingers and toes (2).

The pathophysiology of AD can be attributed to the complex interactions between various susceptibility genes, host environments, infectious agents, defects in skin barrier function, and immunologic responses (3). Characteristic skin inflammatory response is the activation of T lymphocytes, dendritic cells, macrophages, keratinocytes, mast cells, and eosinophils. Typical inflammatory infiltrates within the acute skin lesions have predominantly CD4⁺ T cells, which express CD25 and HLA-DR on their surface, whereas macrophages dominate the dermal mononuclear cell infiltrate in chronic AD lesions (4-5). Clinical improvement is associated with a reduced number of activated skin-infiltrating T cells after therapy with topical calcineurin inhibitors (TCIs), which specifically target activated T cells, corroborates that AD occurs because of T cell-mediated skin inflammation (6).

Interleukin-16 (IL-16) is a cytokine and a potent agent for CD4⁺ cells, including CD4⁺ T cells and CD4-bearing eosinophils *in vitro* (7). The upregulation of IL-16 mRNA expression in acute AD is associated with an increased number of CD4⁺ T cells, suggesting that IL-16 plays a role in the initiation of skin inflammation in AD (8).

To our knowledge, there were only five articles in the literature evaluating the role of IL-16 as a serological marker of disease activity in AD, 3 in adults and 2 in children respectively (9-13). Among studies on adult AD, different authors reached the same conclusion that serum IL-16 levels correlated well with disease severity of AD before and after treatment (11-13). However, conflicting data exists regarding IL-16 as a serum marker to predict the disease activity of AD in children (9-10). Serum eosinophil cationic protein (ECP), total immunoglobulin E (total IgE) and total eosinophil counts (TEC) are evaluated as serum parameters in monitoring the disease activity of AD in children or infancy (14-17). However, little information is available concerning the correlation between these serum parameters.

This study aims to further clarify the potential role of IL-16 as a marker of disease activity in children with AD and to compare the significance

of IL-16, ECP, TEC and total IgE in reflecting AD disease activity in pediatric patients by simultaneous monitoring of their serum levels and correlating them with a standard clinical severity score, Severity Scoring of Atopic Dermatitis (SCORAD index) (18). Correlations between these serum parameters were also analyzed.

MATERIALS AND METHODS

Study population

Forty-eight patients with moderate to severe atopic dermatitis in the acute stage were enrolled in this study. All participants fulfilled the diagnostic criteria of atopic dermatitis defined by Haniffin and Rajka (19). Patients with acute exacerbations of asthma and/or allergic rhinitis necessitating systemic corticosteroids were excluded. Disease severity was measured by the SCORAD index of European Task Force on Atopic Dermatitis

The patients were treated with topical emollients, topical corticosteroids, topical immunomodulators (tacrolimus or pimecrolimus), antihistamines and systemic corticosteroids according to the level of disease severity. The same pediatrician monitored the patients on the initial visit (week 0) and 8 weeks later (week 8) using the SCORAD index and obtaining blood samples for measurement of serum disease activity parameters.

Twenty healthy individuals without personal or family history of atopic disease, including AD, bronchial asthma or allergic rhinitis acted as controls in this study. All patients or their guardians provided written informed consent, and the Institutional Review Board of Taipei Veterans General Hospital approved the study protocol.

Evaluation of disease activity parameters

Peripheral blood samples from the 48 study patients were collected for evaluation at week 0 and week 8. All sera collected were stored at -80°C until analysis. The TEC was obtained using the *Coulter LH 750* hematology analyzer (*Beckman Coulter*, Fullerton, CA, USA), while serum levels of IL-16 were determined by quantitative sandwich enzyme-linked immunosorbent assay, according to the manufacturer's instructions (R&D system, Minneapolis, MN, USA) using a 96-well microplate precoated with murine monoclonal antibody against IL-16. All assays were performed in duplicate. The detection limit of this test kit was 2.7 pg/mL. Serum ECP and total IgE were measured by UniCAP FEIA (Pharmacia Diagnostics AB, Uppsala, Sweden).

Statistical analysis

The Mann-Whitney U test was performed to compare

disease activity parameters between AD patients and healthy controls. Severity scores and serum parameters during disease flare-ups and after resolution of the clinical findings were computed and their differences were compared using the Wilcoxon matched-pairs, signed-ranks test. Pearson's correlation analysis was carried out to determine a possible correlation between the IL-16 value and the clinical severity scores of total SCORAD index and other serum parameters including total IgE, ECP, and peripheral eosinophil counts both in the exacerbation status and after conventional treatment. Data were expressed as mean $\pm$ SEM unless otherwise indicated. A p value < 0.05 was considered statistically significant.

RESULTS

Of the 48 patients (22 females and 26 males with mean age of 7.91 ± 3.34 years: range, 2.5-15 years), most (43/48; 89%) had elevated serum levels of total IgE (mean, 2318 IU/mL; range, 237-5000 IU/mL). Sera from patients (45/48; 93.75%) were positive (specific IgE antibodies >0.35 kU/L) against at least one of the following six common allergens measured by a commercial Pharmacia CAP system (Pharmacia Diagnosis AB, Uppsala, Sweden): house dust mites (*Dermatophoides pteronyssinus* and *Dermatophagoides farinae*), dog dander, cat dander,

milk, and egg white.

Change of disease activity and serum parameters in patients with atopic dermatitis

The mean value of SCORAD scores decreased significantly following treatment starting at 58.5 ± 2.2 at week 0 and dropped to 34.6 ± 2.4 at week 8 ($p < 0.001$) (Table I). At the beginning of the study, the serum levels of IL-16 in patients were 256 ± 22.6 pg/ml, which decreased to 132.5 ± 6.8 pg/ml after treatment ($p < 0.001$). The serum total IgE decreased from 2365 ± 277.6 IU/ml to 2109 ± 271.5 IU/ml ($p=0.002$). The serum ECP levels decreased from 42.5 ± 5.3 μ g/L to 19.5 ± 3.1 μ g/L ($p<0.001$). The TEC decreased from 901.8 ± 129 counts/ μ l to 743.7 ± 78.3 counts/ μ l ($p=0.064$).

Serum levels of IL-16 and ECP in patients with atopic dermatitis compared to healthy controls

Serum levels of IL-16 (Fig. 1a) in AD patients in exacerbation (255.9 ± 22.6 pg/ml) and in resolution (132.5 ± 6.8 pg/ml) were both significantly higher than the healthy controls (90.1 ± 3.2 pg/ml) ($p<0.001$ and $p=0.001$, respectively). Serum levels of ECP (Fig. 1b) in AD patients in exacerbation (42.5 ± 5.3 μ g/L) and in resolution (19.5 ± 3.1 μ g/L) were both higher than those of healthy controls (6.4 ± 0.74 μ g/

Table I. Changes of disease activity and serum parameters in AD patients.

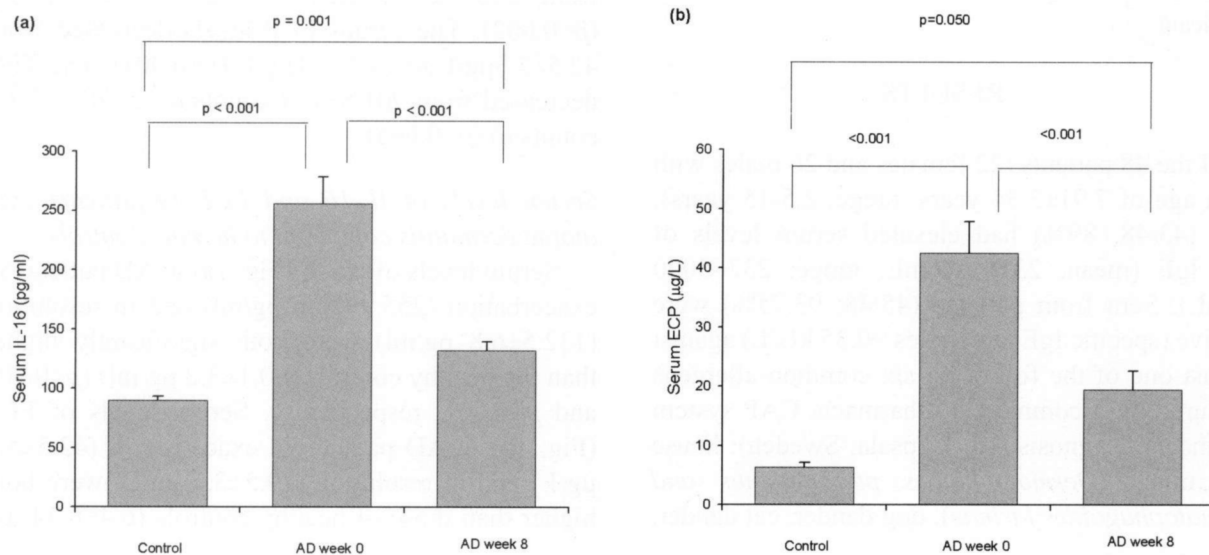
	Baseline (Mean $\pm$ S.E.M) Median (min-max)	Week 8 (Mean $\pm$ S.E.M) Median (min-max)	p value
SCORAD	58.5 ± 2.2 58.2 (30.6-96.0)	34.6 ± 2.4 32.8 (9.7-83.3)	$<0.001^*$
Total IgE (IU/mL)	2365 ± 277.6 1943 (7-5000)	2109 ± 271.5 1284 (8-5000)	0.002*
Total esophil count (count/ μ l)	901.8 ± 129.0 710 (100-5700)	743.7 ± 78.3 594 (40-2684)	0.064
ECP (μ g/l)	42.5 ± 5.3 34.5 (2-133)	19.5 ± 3.1 9.1 (2.0-88.6)	$<0.001^*$
IL-16 (pg/ml)	256 ± 22.6 209.9 (81.7-910.6)	132.5 ± 6.8 134.4 (50-217.8)	$<0.001^*$

* $p<0.05$ by Wilcoxon rank signed test

Table II. Correlation analysis between serum parameters and disease activity (Severity of Atopic Dermatitis [SCORAD]) in the exacerbation (Week 0) and maintenance phases (Week 8).

	SCORAD Week 0		SCORAD Week 8	
	r	p	r	p
Serum IgE (U/ml)	0.317	0.028*	0.510	<0.001†
Total Eosinophil Count(/ μ l)	0.434	0.002†	0.489	<0.001†
Serum ECP(μ g/l)	0.251	0.085	0.468	0.001†
Serum IL-16 (pg/ml)	0.321	0.026*	0.123	0.404

* $p < 0.05$ † $p < 0.01$

**Fig. 1.** Interleukin-16 (a) and eosinophil cationic protein (ECP) (b) in the serum of atopic patients in acute exacerbation phase (W0) and maintenance phase (W8) compared with healthy controls.

L) ($p < 0.001$ and $p = 0.05$, respectively).

Correlation analysis between the disease activity and serum parameters

The association of disease activity reflected by the SCORAD index and serum parameters in patients with AD during the exacerbation phase and maintenance phases after treatment were examined (Table II). There was a positive correlation between the SCORAD and serum IgE in both phases ($r = 0.317$, $p = 0.028$ and $r = 0.510$, $p < 0.001$ in the acute and maintenance phases, respectively). There was also a positive correlation between the SCORAD and TEC in both phases ($r = 0.434$, $p = 0.002$ and $r = 0.489$, $p < 0.001$ in the acute and maintenance phases, respectively). The correlation between the

SCORAD and IL-16 was noted only in the acute phase ($r = 0.321$, $p = 0.026$). The correlation between the SCORAD and ECP was also noted only in the maintenance phase ($r = 0.468$, $p = 0.001$).

Correlation analysis between serum IL-16, total IgE level, total eosinophil counts, and ECP

The positive correlation of serum IL-16 and TEC was noted in the acute phase ($r = 0.463$, $p = 0.001$) (Fig. 2a) but not in the maintenance phase. There was also a positive correlation of ECP and TEC in both phases ($r = 0.317$, $p = 0.028$ and $r = 0.610$, $p < 0.001$ in the acute and maintenance phases, respectively) (Fig. 2b and 2c). Positive correlation of total IgE and ECP was also noted in both phases ($r = 0.399$, $p = 0.005$ and $r = 0.497$, $p = 0.008$ in the acute and maintenance

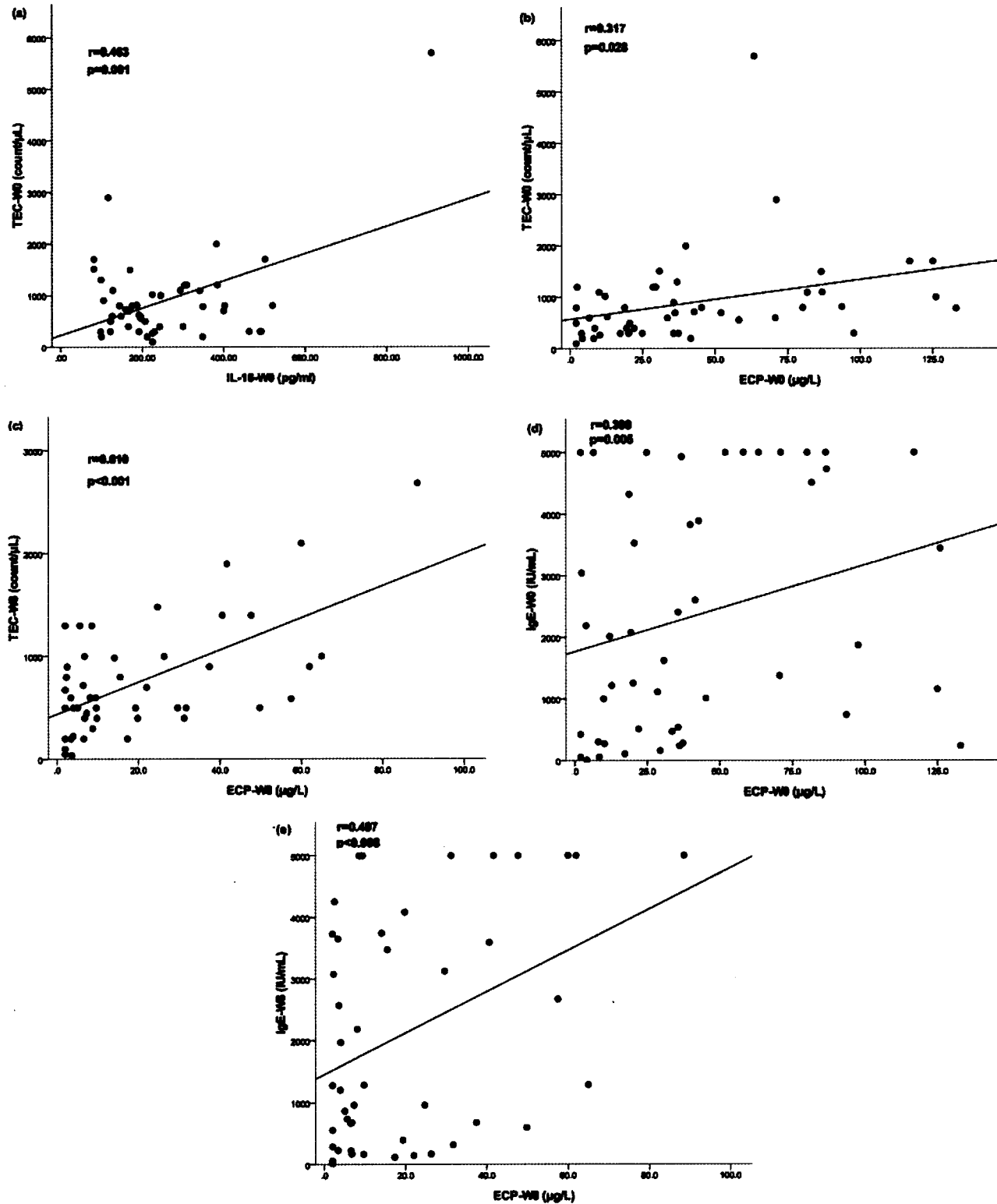


Fig. 2. Correlation of IL-16 and other serum parameter in the acute exacerbation phase (W0) and maintenance phase (W8). *a)* IL-16 and TEC in acute exacerbation phase. *b)* ECP and TEC in acute exacerbation phase. *c)* ECP and TEC in maintenance phase. *d)* Total IgE and ECP in acute exacerbation phase. *e)* Total IgE and ECP in maintenance phase.

phases, respectively) (Fig. 2d and 2e). However, there was no clear correlation among the IL-16 serum levels, ECP, and total IgE (data not shown).

DISCUSSION

IL-16 plays a role in the exacerbation of the disease process in AD. IL-16, synthesized by a variety of immune and non-immune cells, has a patho-biological relevance to the onset and chronicity of AD (20). The production and timing of the release of bioactive IL-16 vary depending on the cell of origin. For example, unstimulated CD8⁺ T cells and mast cells contain processed bioactive IL-16 whose release can be triggered within one to four hours by a variety of stimuli such as histamine, antigen, serotonin, granulocyte-monocyte colony stimulating factor (GM-CSF), phorbol myristate acetate (PMA), and C5a. In contrast, CD4⁺ T cells, dendritic cells (DCs), eosinophils, and fibroblasts constitutively generate the pro-IL-16 protein that is processed and secreted as bioactive IL-16 approximately 12-24 hours after stimulation with either a mitogen, an antigen, IL-4, GM-CSF, IL-1 β or transforming growth factor- β (TGF- β) (21). It serves as a natural ligand of CD4 molecules and induces chemotaxis in CD4-expressing cells such as T cells, eosinophils, dendritic cells, and monocytes (20).

The upregulation of IL-16 mRNA expression in acute AD is associated with increased numbers of CD4⁺ cells, thereby corroborating that IL-16 initiates skin inflammation in AD through recruitment of CD4⁺ cells (8). It also amplifies the inflammatory reaction by stimulating cytokine production in monocytes (22) and by activating T cells (23). The activation of T cells, dendritic cells (DCs), macrophages, keratinocytes, mast cells, and eosinophils are characteristic of AD skin inflammatory responses (24). These findings corroborate that IL-16 plays a role in the exacerbation of AD.

Serum levels of IL-16 are significantly higher in pediatric AD (9-10) and adult AD (11-13) than in healthy controls. These levels decline significantly after treatment and show high correlation with disease severity as assessed by different scales, including the severity scoring of atopic dermatitis (SCORAD), objective severity assessment of atopic dermatitis score (OSAAD), and eruption score in

adult patients (11-13). However, conflicting data exist regarding IL-16 level as a reliable marker of disease activity in children with AD. Frezzolini et al. suggested that IL-16 could serve as a useful marker of disease activity in childhood atopic/eczema dermatitis syndrome (AEDS) before treatment (9), while Fortina et al. found that serum IL-16 levels, although elevated in children with AD compared to healthy controls, did not seem to correlate with disease activity before and after treatment (10). Our study results show positive correlation of serum IL-16 levels with SCORAD in acute exacerbation phase, but not in convalescent phase, which is in accordance with the results reached by Frezzolini et al. (9). The positive correlation between serum IL-16 levels and disease activity makes it a suitable serum parameter for monitoring disease activity in childhood AD. Interestingly, the correlation between serum IL-16 and other predictors of disease in AD [serum IgE, eosinophils (11), sCD30 (9), macrophage-derived chemokines (MDC) (12)] are also observed in these studies.

This study results confirmed the correlation between serum IL-16 levels and disease activity assessed by SCORAD index, as well as the correlation between serum IL-16 levels and TEC in the acute exacerbation phase. Allergen-induced IL-16 production by eosinophils (25) and the recruitment of more eosinophils by IL-16 through the induction of IL-4 release (26) may clarify the correlation between serum IL-16 levels and TEC in peripheral blood.

Eosinophils play a major role in AD, as characterized by activated eosinophils present in the peripheral blood and in the lesional skin (27). The eosinophil cationic protein is a cytotoxic agent secreted by activated eosinophils during allergic and inflammatory responses. Patients with AD have significantly higher levels of serum ECP (14, 17) and peripheral eosinophil count (16-17) compared to healthy controls. This study confirms the positive correlation between serum ECP and TEC with disease activity, as reported in previous studies, and the positive correlation between ECP and TEC (15-16, 28). However, there is no correlation observed between the serum IL-16 and serum ECP. Significant correlation between the severity of atopic dermatitis and serum IgE level has been reported in previous

studies (29-32). The results here confirm the correlation of serum IgE level with disease activity in both the acute exacerbation and maintenance phases. Although we did not analyze the association between allergen-specific IgE levels and SCORAD, Hon et al, in their recent study conclude that the number of common food allergens sensitized correlated with disease severity of AD, extent, and total IgE levels. IgE sensitization to beef protein is unlikely in the majority of Chinese children with AD, but its serum IgE level is associated with disease activity and risk of sensitization to other foods (33).

The decline of serum parameters (i.e. total IgE level, TEC, ECP, and IL-16) with clinical improvement after treatment make them suitable as markers for monitoring AD activity. Their elevated levels in AD patients compared to healthy controls indicate that they participate in the pathogenesis of AD and make them potential targets in therapeutic strategy of AD, including anti-eosinophil therapies by suppressing IL-5 synthesis with glucocorticoids, calcineurin inhibitor or anti-IL-5 antibody (34-35). Omalizumab, is a humanized monoclonal anti-IgE antibody that binds to the IgE molecule at the high-affinity receptor binding site, significantly reducing the amount of free IgE circulating in serum. Treatment with omalizumab shows a significant decrease in AD severity in several trials (36-37). Suppression of IL-16 expression in Langerhan's cells and inhibiting its production may be the next investigating option of treatment in AD.

In conclusion, serum levels of total IgE, IL-16, serum ECP, and TEC show positive correlations with the disease activity of childhood AD and can serve as serum markers in predicting disease activity. The decreases in these serum parameters may be used as monitors of the clinical improvement.

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