

Association of serum interleukin-18 and other biomarkers with disease severity in adults with atopic dermatitis

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Abstract Atopic dermatitis (AD) is a chronic inflammatory disease of the skin for which there are no reliable biomarkers to assess clinical severity. Serum interleukin-18 (IL-18) levels may be associated with AD severity. To identify putative biomarkers associated with clinical severity in adult AD patients, we enrolled 121 adult AD patients (mean age 35.7 years) and 50 healthy controls (mean age 31.7 years). We compared these groups for blood eosinophils and serum levels of IL-18, thymus and activation-regulated chemokine (TARC), total IgE, and lactate dehydrogenase (LDH). We also determined *S. aureus* enterotoxin B (SEB) specific IgE levels and the SCORingAD (SCORAD) scores for AD patients. For AD patients, stepwise logistic regression was used to estimate odds ratios (OR) for each biomarker for the likelihood of having AD, and multiple linear regression was used to identify biomarkers associated with SCORAD scores. Compared with healthy controls, adult

AD patients had higher levels of IL-18, TARC, total IgE, eosinophils, and LDH. TARC levels had the highest OR for AD occurrence, while the OR for IL-18 was insignificant. Also, IL-18 was not related to the presence of SEB-IgE. Notably, IL-18 levels were significantly associated with SCORAD scores, as were TARC, total IgE, and LDH levels. A panel of biomarkers (IL-18, TARC, total IgE, and LDH) may be more useful to accurately assess clinical severity in adult AD patients.

Keywords Interleukin 18 · Thymus and activation-regulated chemokine · Immunoglobulin E · Eosinophils · Lactate dehydrogenase · SCORingAD · Adult atopic dermatitis

Introduction

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease that affects nearly 3% of Japanese adults [22]. The pathogenesis of AD is mediated, in part, by CD4 T lymphocytes that produce a type 2 helper T cell (Th2) cytokine profile [4, 5]. This implies that AD results from an aberrant adaptive immune response. Yet, the underlying pathogenesis of AD remains largely unknown, and recent evidence suggests that elements of both the innate and adaptive immune systems may play roles in the development of AD [32].

Interleukin (IL)-18, also called interferon (IFN)- γ -inducing factor, was originally considered a type 1 helper T cell (Th1) cytokine that induced IFN- γ production [24]. However, recent studies have indicated a more complex pleiotropic role for IL-18, and IL-18 appears to be an important regulator in both innate and acquired immune responses [34]. IL-18 can induce the production of immunoglobulin E (IgE) and

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Th2 cytokines by antigen-stimulated helper T cells [9, 31]. In addition, mice that produced abundant IL-18 could develop AD-like lesions independently of an IgE response [17, 33]. These results indicate that IL-18 is associated with the pathogenesis of AD.

Serum IL-18 has been found to be associated with AD severity, mainly in children and some adults [8, 26, 28] although the numbers of patients evaluated were limited. We recently reported elevated levels of IL-18 in the stratum corneum of AD patients, which presumably reflected IL-18 production by keratinocytes [10]. However, no previous studies have evaluated serum IL-18 levels in the clinical management of adult AD patients. In addition, there are currently no reliable biomarkers to clinically monitor adult AD [15, 29], which may have both innate and adaptive immune components. Also, no previous study of AD patients has evaluated possible relationships of serum IL-18 levels with other biomarkers or changes over time in serum IL-18 levels accompanying changes in clinical AD symptoms.

In this study, we monitored blood eosinophil counts and the serum levels of thymus and activation-regulated chemokine (TARC), total IgE, and lactate dehydrogenase (LDH), as commonly used AD biomarkers. We also monitored serum IL-18 levels and investigated possible associations between serum IL-18 and both clinical severity and other serum biomarkers during the clinical course in adult AD patients. Furthermore, we previously demonstrated an association between *Staphylococcus aureus* colonization with IL-18 in AD patients [10]; thus, we also investigated associations between *S. aureus* enterotoxin B (SEB)-specific IgE and AD-related biomarkers. From our results, we suggest that serum IL-18 will become an important biomarker for follow-up and assessment of treatment in adult AD patients. Our results also suggest that a panel of biomarkers, including IL-18, TARC, total IgE, and LDH, is more reliable for monitoring AD clinical severity in adults than any single marker.

Methods

Subjects and assessments of clinical conditions

This was a prospective study that was conducted from January 2008 to January 2011. This study included 121 adult AD patients (mean age 35.7 years; age range 18–75 years) and 50 healthy volunteers as controls (mean age 31.0 years; age range 22–50 years). Patients were diagnosed with AD by dermatologists according to the criteria of Hanifin and Rajka [6]. All AD patients were treated with topical corticosteroids according to the criteria in the therapeutic guidelines for atopic dermatitis of 2002 [20], in addition to moisturizers and oral antihistamines as needed. The healthy controls met the following criteria: normal serum total IgE

levels; no personal or family history of atopic dermatitis, asthma, allergic rhinitis, or allergic conjunctivitis; and no symptoms of erythema, eczema, or pruritis.

At the time of enrollment, all AD patients and healthy controls had blood drawn by sterile venipuncture for baseline determinations of blood eosinophil counts and serum concentrations of IL-18, TARC, total IgE, and LDH. AD patients were also tested for serum *S. aureus* enterotoxin B-specific IgE.

Atopic dermatitis patients were also evaluated for general disease severity using the SCORingAD (SCORAD) index [18]. Atopic dermatitis severity was categorized based on SCORAD values as: mild (SCORAD <30); moderate (SCORAD = 30–60); or severe (SCORAD ≥60).

Written informed consent was obtained from all AD patients and healthy controls. All study protocols were approved by the ethics committee of Yokohama City University School of Medicine (Approval No. B090312014).

Cyclosporine A treatment

A total of 24 AD patients, including 3 with moderate and 21 with severe AD at baseline (week 0), received cyclosporine treatments for 8 weeks. These patients took 3 mg/kg cyclosporine A orally, twice a day (before breakfast and before dinner). After 8 weeks, cyclosporine administration was stopped because of Japanese National Health Insurance regulations. During the 8 weeks of cyclosporine therapy, no changes were made in patients' other medications.

Serum levels of IL-18, TARC, total IgE, and LDH and blood eosinophil counts were determined before starting cyclosporine A treatment (week 0, baseline), at 2, 4, and 8 weeks after starting treatment, and again at onset of recurrence (after cyclosporine A was stopped). SCORAD scores were also recorded at these time points.

ELISAs for serum IL-18, TARC, and total IgE

Serum samples were obtained from clotted blood after centrifugation at $2,330\times g$ for 10 min at 4°C and then stored at –80°C until analysis. Commercial ELISA kits were used according to the manufacturers' instructions to determine serum levels of IL-18, TARC, and total IgE. These included: a human IL-18 ELISA kit (MBL, Nagoya, Japan) with a lower detection limit of 12.5 pg/mL; a human TARC ELISA kit (Shionogi, Osaka, Japan) with a lower detection limit of 125 pg/mL; and a human IgE sandwich electrochemiluminescence immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany) with a lower detection limit of 0.10 IU/mL.

As a note on IL-18 measured in this study, IL-18 can be found as either a biologically inactive, 24-kDa “immature” form (pro-IL-18) or a biologically active, 18-kDa “mature”

Table 1 Baseline characteristics for the control and atopic dermatitis (AD) groups

	Control group (<i>n</i> = 50)	AD group (<i>n</i> = 121)	<i>P</i> value
Age, years	30.5 (28, 36)	35 (25, 43)	0.047
Gender			0.717
Males, <i>n</i> (%)	27 (54.0)	69 (57.0)	
Females, <i>n</i> (%)	23 (46.0)	52 (43.0)	
Age of AD onset, years	ND	6 (3, 11)	NA
SCORAD scores	ND	42 (24.9, 64.0)	NA
AD severity ^a			NA
Mild	ND	41 (33.8)	
Moderate	ND	40 (33.1)	
Severe	ND	40 (33.1)	
IL-18 (ng/ml)	0.13 (0.11, 0.17)	0.24 (0.18, 0.37)	<0.001
TARC (ng/ml)	0.25 (0.24, 0.26)	1.48 (0.64, 3.54)	<0.001
IgE (ng/ml)	0.21 (0.14, 0.30)	3.28 (0.91, 10.80)	<0.001
Eosinophils (counts/ μ l)	166.50 (99.75, 236.25)	497.80 (271.13, 779.03)	<0.001
LDH (IU/L)	189.50 (162.75, 206.25)	243.50 (205.75, 284.00)	<0.001

^a AD severity was categorized as mild (SCORAD < 30), moderate (SCORAD = 30–60), severe (SCORAD $\geq$ 60)

Results for gender are given as *n* (%) and compared using a Chi-square test. Results for other continuous variables are given as median (IQR: Q1, Q3) and compared using a Mann–Whitney *U* test

form (IL-18). Pro-IL-18 is converted to IL-18 by cleavage of an aspartic acid at position P1 by an intracellular cysteine protease, IL-1 β converting enzyme (ICE; Caspase-1), and this “mature” form is readily released by cells [23]. In this study, 99.3% of the IL-18 assayed was in the “mature” form.

Assays for LDH, eosinophils, and SEB-specific IgE

Our hospital’s Clinical Laboratory Services did the determinations for serum LDH levels, blood eosinophil counts, and SEB-specific IgE levels. Serum LDH was determined using an international federation of clinical chemistry LDH assay kit (Roche Diagnostics GmbH, Mannheim, Germany), with results reported as IU/L. Blood eosinophil counts were determined using a LH 700 Series Hematology Analyzer (Beckman Coulter, Inc., Brea, FL, USA), with results reported as numbers/ μ L. Serum SEB-specific IgE was determined using a UniCAP 1000 (Phadia, Tokyo, Japan), with positive results reported for levels >0.70 UA/mL.

Statistical analysis

All statistical analyses used SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA). For the AD and control groups, results for gender are given as *n* (%) and compared using a Chi-square test. Results for study subjects’ continuous baseline variables are given as medians with 1st and 3rd inter-quartiles (IQR: Q1, Q3) and compared using Mann–Whitney *U* tests due to their non-normal distributions.

For AD patients only, stepwise logistic regression was performed for those variables that had *P* values <0.2 in univariate analysis and were selected for multiple logistic regression analysis. Odd ratios (OR) with corresponding 95% confidence intervals (95% CI) were estimated to deter-

mine associations between AD and AD related markers. Spearman’s correlation analysis was used to assess associations among AD related markers. Those variables with significant correlations with SCORAD scores were entered into multiple linear regression analysis using stepwise selection. The multiple linear regression analysis provided estimated regression coefficients (β) and their corresponding 95% CIs.

For AD patients that received cyclosporine A treatment, the differences in AD-related markers relative to the baseline values were compared using Wilcoxon sign-rank tests, except for LDH analyzed by paired *t* test.

All statistical assessments were two-tailed and considered significant at *P* < 0.05.

Results

Subjects’ baseline characteristics

A total of 171 subjects were enrolled in this study: 50 healthy volunteers (control group) and 121 adult patients with atopic dermatitis (AD group). Table 1 summarizes these subjects’ baseline characteristics. On average, patients in the AD group were slightly older than the subjects in the control group, but the proportions of males versus females in both groups were equivalent.

In the AD group, the median age of disease onset was 6 years (IQR: 3, 11 years), indicating that they did not have adult-onset AD. Their median baseline SCORAD score was 42 (IQR: 24.9, 64.0). Among the AD patients, 41 had mild AD, 40 had moderate AD, and 40 had severe AD. At baseline, the blood eosinophil counts, and serum concentrations of TARC, total IgE, and IL-18 were significantly higher in the AD group compared with the control group (Table 1).

Table 2 Associations between AD occurrence and AD related markers through stepwise logistic regression analysis^a

Variables ^b	OR [95% CI].	P value
IL-18	3.84 [0.587, 25.126]	0.160
TARC	37.75 [1.514, 941.631]	0.027
IgE	2.72 [1.186, 6.256]	0.018
Eosinophils	1.01 [0.997, 1.014]	0.241
LDH	0.98 [0.952, 1.014]	0.284

Abbreviations: see footnote in Table 1. OR odds ratio, 95% CI. 95% confidence intervals

^a Stepwise logistic regression was done as described in “Methods”

^b IL-18, TARC, and IgE values were transformed with natural logarithms prior to the analysis

Table 3 Correlations between baseline SCORAD, IL-18, TARC, IgE, eosinophils, and LDH for AD patients (N = 121)

^a Correlation coefficient	IL-18 (ng/ml)	TARC (ng/ml)	IgE (ng/ml)	Eosinophils (counts/ μ l)	LDH (IU/L)
SCORAD	0.472***	0.794***	0.305**	0.459***	0.454***
TARC	0.604***	–			
IgE	0.264**	0.355***	–		
Eosinophils	0.386***	0.513***	0.326***	–	
LDH	0.459***	0.519***	0.185*	0.462***	–

Abbreviations: see footnote in Table 1

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, indicated significantly correlation

^a Results are Spearman correlation coefficients

Biomarker associations with AD in adults

For AD patients, those variables with a P value < 0.2 from the univariate analyses in Table 1 were selected and entered into multiple logistic regression analysis. Table 2 shows the results of stepwise logistic regression analysis for the associations between putative AD-related markers and having AD. After adjusting for subjects' age, this stepwise logistic regression analysis showed that subjects with increased levels of TARC and total IgE might be at higher risk of having AD (Table 2).

Table 3 shows all of the correlation results among baseline SCORAD scores, IL-18, TARC, total IgE, eosinophils, and LDH in the AD group. In the AD group, the baseline levels of most of these AD-related markers were positively correlated with each other.

Table 4 shows the results of multiple linear regression analysis for the AD group with SCORAD scores as the dependent variable. Variables that were significantly correlated with SCORAD scores (Table 3) were selected and entered as predictors into multiple linear regression analysis using stepwise selection. These results showed that the SCORAD values would be increased by 31.55 [95% CI: 2.53–60.58] when the IL-18 level increased by 1 unit (1 ng/ml). Similarly, SCORAD

Table 4 Multiple linear regression analysis with SCORAD as dependent variable for AD patients (N = 121)

Predictors	β [95% CI for β]	P value
IL-18	31.55 [2.525, 60.576]	0.033
TARC	0.61 [0.149, 1.077]	0.010
IgE	0.47 [0.192, 0.744]	0.001
LDH	0.08 [0.031, 0.137]	0.002

Multiple linear regression analysis using stepwise selection was done as described in “Methods”. Eosinophil counts were excluded from the stepwise selection

Abbreviations: see footnote in Table 1

Table 5 Comparisons of AD-related markers based on the presence of SEB (*Staphylococcus aureus* enterotoxin B)-specific IgE antibody

	SEB IgE		P value
	Negative	Positive	
	56	53	
IL-18 (ng/ml)	0.235 (0.175, 0.332)	0.260 (0.189, 0.410)	0.258
TARC (ng/ml)	1.018 (0.494, 2.143)	1.988 (0.973, 5.308)	0.007
IgE (ng/ml)	1.429 (0.465, 3.488)	9.604 (3.281, 17.329)	< 0.001
Eosinophils (counts/ μ l)	469.20 (226.80, 667.80)	585.90 (330.05, 901.20)	0.029
LDH (IU/L)	240 (202, 273)	252 (212, 321)	0.201

Results are median (IQR: Q1, Q3). SEB (*Staphylococcus aureus* enterotoxin B)-specific IgE antibody was recorded as positive for levels > 0.70 UA/ml. Group comparisons were by Mann–Whitney U test

Abbreviations: see footnote in Table 1

values would be increased by 0.61 [95% CI: 0.15–1.08] if the TARC level increased by 1 unit (1 ng/ml), would be increased by 0.47 [95% CI: 0.19–0.74] if the total IgE level increased by 1 unit (1 IU/ml), and would be increased by 0.084 [95% CI: 0.03–0.14] if the LDH level increased by 1 unit (1 IU/L). Eosinophil counts did not have a significant relationship to SCORAD scores in this analysis. Thus, these results suggest that a combination of IL-18, TARC, total IgE, and LDH may be useful panel of biomarkers for screening adult AD patients with regard to their AD severity.

Table 5 shows the comparisons of AD related-markers based on the presence or absence of SEB-specific IgE antibodies. Among the 121 AD patients, 53 were positive for SEB-specific IgE, 56 were negative for SEB-specific IgE, and 12 AD patients were not tested for SEB-specific IgE. Patients who were positive for SEB-specific IgE had higher TARC and total IgE levels than those who were negative for SEB-specific IgE.

Changes in AD severity and biomarkers in adults receiving cyclosporine A

We investigated associations between disease severity and the levels of AD-related biomarkers in patients whose

disease severity was modulated by cyclosporine A treatment. As described in “Methods”, a total of 24 AD patients, including 3 with moderate and 21 with severe AD at baseline (week 0), received cyclosporine A treatment for 8 weeks. Figure 1 shows the changes in AD-related markers, including SCORAD values, IL-18, TARC, total IgE, eosinophils, and LDH before cyclosporine A therapy (week 0); during cyclosporine therapy (at weeks 2, 4, and 8); and at AD exacerbation (after cyclosporine A was stopped). There was a significant decrease in SCORAD values during cyclosporine A therapy. SCORAD scores increased again with AD exacerbation (Fig. 1a). We also found significant decreases in the levels of other AD-related markers (except for total IgE levels) during cyclosporine A therapy and increases in these markers upon AD exacerbation (Fig. 1b–f).

After 2 weeks of cyclosporine A therapy, 2, 13, and 9 of these 24 patients had mild, moderate, and severe AD, respectively. At week 4 of cyclosporine A therapy, 12, 9, and 3 patients had mild, moderate, and severe AD, respectively, and at week 8 of cyclosporine A therapy, 16, 8, and 0 patients had mild, moderate, and severe AD, respectively. We found that 66.7% (18/24) of these patients had mild AD at week 8 of cyclosporine A therapy. Notably, AD severity worsened when these patients stopped taking cyclosporine A (at exacerbation).

Yet, in light of the results shown in Table 4, a panel of serum biomarkers, including IL-18, TARC/CCL17, total IgE, and LDH could be useful for assessing clinical severity and therapeutic efficacy for adult AD patients.

Discussion

The results of the present study showed that serum IL-18 concentrations in adult AD patients were significantly increased compared with those of healthy adult controls. Serum IL-18 levels were also correlated with AD clinical severity. Furthermore, serum IL-18 levels were positively correlated with other biomarkers commonly used to assess AD severity, including serum TARC, peripheral blood eosinophils, and serum LDH. During cyclosporine A treatment, decreases in serum IL-18 levels paralleled the improvements in AD clinical severity and decreases in the levels of other biomarkers. Thus, serum IL-18 levels may play some role in monitoring AD clinical severity, although, due to the complex pathophysiology of AD that may involve elements of both the innate and adaptive immune systems [32], the utility of a single biomarker must be considered in context.

Several investigations have reported links between serum IL-18 concentrations and AD severity, but the sample sizes were small and the strengths of association varied [8, 28].

These studies focused mostly on pediatric AD patients, and adult patients have not been sufficiently investigated. We investigated serum IL-18 levels in 121 AD patients, all of whom were adults (mean age 35.7 years). Our results for the relationship between AD and IL-18 support previous findings [8, 28], which indicates that monitoring serum IL-18 levels could help clinicians evaluate AD severity in both pediatric and adult patients.

We also examined the relationships between serum IL-18 levels and other AD biomarkers. TARC is now frequently used as a marker of AD severity in Japan because of its close correlation with AD severity [12, 27], and our study found a strong correlation between TARC and serum IL-18 levels. Because TARC is produced by T cells, the association between TARC and IL-18 levels suggests involvement of an aberrant adaptive immune response in our adult AD patients. We also found a strong association between serum IL-18 and LDH levels, as in a previous study [21]. LDH is an enzyme that is widely distributed in tissues, including the skin, and is generally elevated due to various disease processes. However, LDH has no known association with innate or adaptive immunity, which again suggests that serum IL-18 levels could serve as an objective index of clinical AD severity.

However, we found no clear relationship between serum total IgE and IL-18 levels, although total IgE levels may be associated with AD severity [11]. In addition, we found no relationship between serum IL-18 levels and SEB-specific IgE. We previously noted that *S. aureus* on the skin may promote the production of IL-18 by keratinocytes of AD patients. However, the extent of this promotion was lower in a group with relatively low total IgE (<1,500 IU/mL) and no correlation was found between the production of IL-18 by keratinocytes and serum IgE levels [10]. Nakanishi et al. [23] reported IL-18 overproduction by keratinocytes and greater AD severity in NC/Nga mice, a murine model of AD, when subjected to repeated application of *S. aureus* protein A (SpA). Colonized *S. aureus* is thus likely to promote IL-18 production and exacerbate AD in the approximately 20% of AD patients with relatively low IgE production.

A previous study found that serum IL-18 levels were related to eosinophil counts but were unrelated to IgE levels in children with AD [25]. We also found an association between IL-18 levels and eosinophil counts, but not total IgE, in our adult AD patients. Tanaka et al. [28] also found that IL-18 was not significantly correlated with IgE. However, recent studies have revealed a pleiotropic role for IL-18. It was reported that IL-18 induced AD-like lesions independently of Th2 or IgE responses in mice producing abundant IL-18 [17, 33].

Depending on the context, IL-18 can promote Th1 and Th2 adaptive immune response [23]. Adding to this complexity, a modular view of cytokine networks proposes

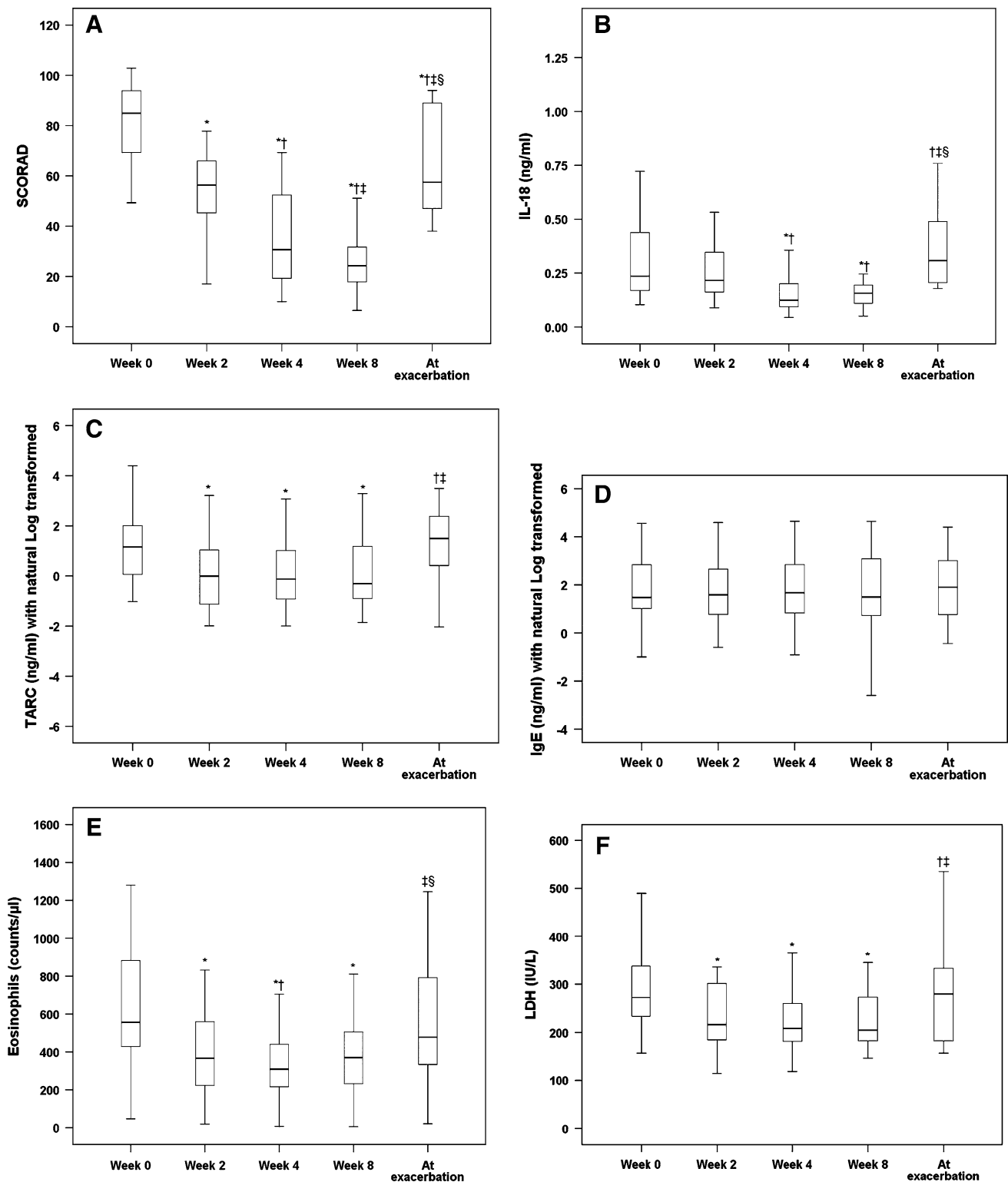


Fig. 1 Changes in AD-related markers over time during cyclosporine A therapy. As described in “Methods”, 24 AD patients received cyclosporine A therapy for 8 weeks. Results are shown as *box-plots* (horizontal lines are median values; error bars are interquartile ranges) before cyclosporine therapy (week 0), during cyclosporine therapy (at weeks 2, 4, and 8), and at AD exacerbation (cyclosporine stopped) for

a SCORAD, **b** IL-18, **c** TARC, **d** IgE, **e** eosinophils, and **f** LDH. Changes from baseline were compared using Wilcoxon sign-rank test, except for LDH results that used paired *t* test. ^{*}[†][‡][§], indicates significantly different as compared with ^{*}week 0, [†]week 2, [‡]week 4, and [§]week 8, respectively. ($P < 0.05$)

that AD may be the consequence of the interactions among three distinct sources of groups of cytokines: (1) keratinocytes, (2) innate immune cells, and (3) T cells [3]. Our results in Table 5 showed clear associations between SEB-specific IgE responses and TARC, total IgE, and eosinophils, all of which are reflective of adaptive immune responses. Again, however, there was no apparent association between SEB-specific IgE and IL-18 levels, or between SEB-specific IgE and LDH levels, yet we found an association between IL-18 and LDH.

In our investigations of AD patients who received cyclosporine A treatments, we found that declines in IL-18 levels paralleled those of clinical severity (SCORAD scores) and markers of adaptive immune responses (TARC levels and eosinophil counts; Fig. 1). Recent studies of cyclosporine A treatment for AD found that the responses were primarily due to activation of adaptive immune responses and, in particular, subsets of regulatory T cells [1, 7, 19]. Furthermore, other recent work has shown that single nucleotide polymorphisms in a promoter of the IL-18 gene [30] and particular IL-18 gene haplotypes [16] are associated with the likelihood of developing AD.

In light of these considerations, although we have found that the serum IL-18 level is associated with AD clinical severity in adults, considerable work needs to be done to determine if IL-18 is more closely associated with innate or adaptive immune responses in AD, what role genetics plays in IL-18's association with AD, and what other regulatory elements are involved with IL-18 production in AD. In this exploratory study, we did not include other assessments of innate immune responses. Also, as this was a single-center study, larger studies in different centers and evaluating patients with different clinical conditions will be needed to confirm our results.

Atopic dermatitis is a refractory, chronically relapsing inflammatory disease of the skin that often defies control [2]. Clinicians seeking to assess the efficacy of AD treatments need objective markers to accurately indicate disease severity. Our study showed that treatment alleviated rash and reduced serum IL-18 levels. This responsiveness was demonstrated by the significant correlation between changes in clinical AD symptoms and serum IL-18 levels over time (Fig. 1). However, as we have already discussed, a single biomarker alone is probably not adequate to reflect the complex pathophysiology of AD.

Our results in Table 2 showed that serum TARC levels exhibited the highest OR for the likelihood of having AD in adults. TARC, currently the biomarker most reflective of clinical symptoms in AD, also increases in bullous pemphigoid [14], mycosis fungoides [13], and other skin diseases. A comprehensive method for evaluating the severity of AD disease with a new AD biomarker or combination of AD biomarkers would, therefore, be clinically useful. Our results

suggest that a panel of biomarkers, including IL-18, TARC, total IgE, and LDH, may be useful for monitoring AD clinical severity. Our findings also highlight the potential of serum IL-18 as a biomarker of AD, suggesting that an anti-IL-18 antibody may be useful in future AD treatment.

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Conflict of interest The authors declare there are no conflict of interest.

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