

Biomarkers for Atopic Dermatitis in Children

Risa Tamagawa-Mineoka, MD, PhD

Numerous studies investigating the correlations between the severity of atopic dermatitis (AD) and various biomarkers have been reported over the past few decades. Recent studies have indicated that certain soluble mediators, including chemokines (such as thymus and activation-regulated chemokine/C-C motif chemokine ligand [CCL]17 and macrophage-derived chemokine/CCL22) and cytokines (such as thymic stromal lymphopoietin), could be good markers of inflammation in AD. This review focuses on circulating biomarkers of AD, including pediatric AD.

Keywords: atopic dermatitis, biomarker, chemokine, cytokine

Introduction

ATOPIC DERMATITIS (AD) is a common allergic skin disease that is caused by genetic and environmental background factors.¹ It is characterized by the disturbance of epithelial barrier function and IgE-mediated sensitization to food and environmental allergens. The condition often begins during infancy or childhood. It is important to determine the severity of AD during its treatment and follow-up in pediatric patients.

There are several disease severity scoring systems for AD, such as the SCORing of Atopic Dermatitis (SCORAD) and Eczema Area Severity Index. However, such subjective scoring systems can be affected by intra and interobserver variations.² A biomarker is by definition a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.³ With regard to the clinical field of AD, biomarkers can be used to measure disease activity, quantify therapeutic efficacy, and predict disease progression.⁴ Because of the ease of accessibility, it is useful to measure circulating biomarkers obtained from blood. This review focuses on circulating biomarkers that can help clinicians understand the skin conditions of AD patients, including pediatric AD.

Chemokines

Considerable amounts of chemokines, such as thymus and activation-regulated chemokine (TARC)/C-C motif chemokine ligand (CCL)17 and macrophage-derived chemokine (MDC)/CCL22, contribute to the infiltration of macrophages, eosinophils, and T cells into acute and chronic AD lesions.¹

TARC/CCL17

TARC is a chemokine that attracts CC chemokine receptor 4 (CCR4)-positive cells. Several studies have shown that children with AD exhibit higher serum levels of TARC than healthy controls.^{5–8} In addition, serum TARC levels are closely correlated with disease severity in children with AD.^{6–8} Similar findings have also been obtained in adult patients with AD.^{8–12} Furthermore, the mean serum level of TARC was shown to be higher in children with sustained AD than in those with regressed AD, indicating that serum TARC levels are correlated with the natural course of childhood AD.⁵ Fujisawa et al. found that among normal individuals, young children, especially those in the 0–1 year age group, display higher serum TARC levels. In addition, they determined the TARC cutoff values for diagnosing AD (1431 pg/mL for the 0–1 year age group, 803 pg/mL for the 2–5 year age group, and 510 pg/mL for the 6 years and older age group).⁷

Keratinocytes, T cells, dendritic cells, and endothelial cells are major sources of TARC in AD patients. Kakinuma et al. detected immunoreactive TARC in the epidermal keratinocytes, dermal infiltrating cells, and endothelial cells present in the lesional skin of adult AD patients in both acute and chronic phases.⁹ In addition, Vestergaard et al. detected TARC-positive cells in the epidermis and CCR4-positive cells in both the dermis and epidermis.¹³ Morphologically, CCR4-positive cells resemble lymphocytes. Interestingly, Morita et al. revealed that TARC levels in the stratum corneum, samples of which were obtained from adult AD patients through tape stripping, were correlated with the severity of local skin lesions, especially with the scores for erythema, edema/papules, and oozing/crusting.¹⁴ The tape-stripping method is easy and safe. Therefore, it might be useful for evaluating disease severity in AD patients.

MDC/CCL22

MDC is another chemokine that attracts CCR4-positive cells. Some studies have shown that AD patients, including pediatric patients, display higher serum MDC levels than healthy controls.^{6,15} In addition, serum MDC levels have been reported to be correlated with disease severity in infants and young children with AD.^{6,16} Leung et al. reported that serum MDC concentrations are more strongly correlated with disease severity than the serum levels of TARC in infants and young children with AD.¹⁶

Cutaneous T cell-attracting chemokine/CCL27

Cutaneous T cell-attracting chemokine (CTACK) acts specifically on CCR10 and is produced by epidermal keratinocytes.¹⁷ Therefore, CTACK is a skin-specific chemokine, while TARC and MDC are not skin specific. Children with AD display higher serum CTACK levels than healthy children.^{6,18} The serum levels of CTACK are closely correlated with disease severity in children with AD^{6,18} as well as adult AD patients.¹⁰ Furthermore, the serum levels of CTACK are correlated with those of TARC and MDC.

Cytokines

Type 2 immune reactions involving increased IgE levels and eosinophilia predominate in AD.¹ Type 2 cytokines, such as interleukin (IL)-4 and IL-5, are produced in the acute phase of AD. In chronic AD lesions, the levels of type 1 cytokines, including interferon- γ and IL-12, are increased.

Thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine that is preferentially produced by epithelial cells, such as keratinocytes and airway mucosal cells.¹⁹ TSLP is strongly expressed by keratinocytes in the lesional skin of AD patients.²⁰ This cytokine is associated with the activation and migration of dendritic cells within the dermis in AD patients.¹ In addition, TSLP induces naïve CD4⁺ T cells to differentiate into Th2 cells.¹ These findings suggest that TSLP is closely involved in the pathogenesis of AD.

Pediatric and adult AD patients exhibit higher serum TSLP levels than healthy subjects.^{21,22} In addition, in examinations of samples of the stratum corneum obtained through tape stripping, it was found that the TSLP expression levels of adult AD patients were markedly higher than those of healthy subjects. Furthermore, the TSLP expression levels in the stratum corneum were shown to be correlated with disease severity, especially the dry skin score and stratum corneum hydration.²³ The TSLP concentrations of serum and the stratum corneum can be used as biomarkers of AD severity, particularly epidermal barrier status.

IL-33

IL-33 is a member of the IL-1 cytokine family and a promoter of type 2 immune reactions.²⁴ Recent reports have described the involvement of IL-33 in the pathogenesis of AD (23–25). Transgenic mice expressing the IL-33 gene develop spontaneous itchy dermatitis with features of AD, such as eosinophil infiltration into inflamed skin and high serum IgE levels.²⁵ The expression of IL-33 is increased in the keratino-

cytes, endothelial cells, and fibroblasts found in the lesional skin of patients with AD.^{26,27} Elevated serum IL-33 levels are seen in children with AD²¹ as well as adult AD patients.^{28–30} In adult AD patients, IL-33 levels are significantly correlated with disease severity, especially the degree of excoriation and the xerosis score.²⁸ However, it has been reported that the present human IL-33 enzyme-linked immunosorbent assay kit might give rise to a high prevalence of false positives if not validated.³¹ Therefore, additional studies with validation steps are needed to examine serum IL-33 levels in AD patients.

IL-18

IL-18 is a pleiotropic cytokine that plays important roles in both type 1 and type 2 immune reactions. IL-18 has the ability to induce interferon- γ production, leading to type 1 immune reactions.³² In contrast, IL-18 can also enhance the production of type 2 cytokines and stimulate the synthesis of IgE.³³ AD adult patients exhibit higher serum IL-18 concentrations than healthy subjects, and serum IL-18 levels have been found to be correlated with the extent of disease and serum IgE levels in AD patients, including pediatric AD patients.^{34–37}

IL-31

Itching represents one of the major symptoms of AD. Itching is often resistant to H1-antihistamine administration in AD patients, suggesting that histamine and other mediators are involved in the mechanisms responsible for itching in AD.³⁸ IL-31 is produced by Th2 cells and regulates itching through a neuronal receptor. It is regarded as the mediator that is most closely related to itching in AD.³⁹ Both pediatric and adult AD patients exhibit higher serum IL-31 levels than healthy controls.^{21,40,41} Furthermore, serum IL-33 levels are correlated with disease severity.^{40,41} However, it has been reported that serum IL-31 levels are not increased in children with AD.⁴² Serum IL-31 levels have been less frequently studied and need further investigations.

IL-17

Recent studies have suggested that Th17 cells are associated with allergic inflammation. However, while some studies have reported that the numbers of Th17 cells are increased in AD patients, other studies have obtained contradictory findings.^{43–46} There are 6 Th17-mediated cytokines (IL-17A to IL-17F). Park et al. detected increased serum IL-17F levels in pediatric AD patients and found that serum IL-17F levels are correlated with disease severity in such children.⁴⁷ Therefore, IL-17F might be a useful clinical biomarker of pediatric AD.

Other soluble biomarkers

Soluble E-selectin

E-selectin is an adhesion molecule that is expressed on activated vascular endothelia. The expression of this molecule in the skin is increased during cutaneous inflammation, including that induced by AD. The soluble form of E-selectin is present in the circulating blood as a result of shedding and is regarded as a biomarker of inflammatory disease. Several previous studies have reported that serum soluble E-selectin levels are elevated in children with AD.^{48–52} In addition, the

serum levels of soluble E-selectin have been shown to be correlated with disease severity in children with AD.^{48–50}

Soluble CD30

The surface antigen, CD30, is a 120-kD membrane-bound glycoprotein belonging to the tumor necrosis factor receptor superfamily. It has been shown that CD30 is an activation marker of T cell clones that produce Th2-related cytokines.⁵³ The soluble form of the molecule is released into the bloodstream after cellular activation. Elevated serum levels of soluble CD30 have been detected in pediatric and adult AD patients.^{54–58} Furthermore, serum soluble CD30 levels are correlated with disease severity in AD patients.^{54–58}

Total IgE

A number of studies have examined the use of the total serum IgE level as a biomarker of AD.⁵⁹ However, in a meta-analysis of both longitudinal and cross-sectional studies, Thijs et al. demonstrated that the total serum IgE level is not an appropriate biomarker for following up disease severity in AD.⁵⁹ On the other hand, Fukiwake et al. observed greater and more rapid increases in total IgE levels in children with long-term AD than in those whose AD had spontaneously regressed.⁶⁰ These findings suggest that the serum IgE level is an appropriate biomarker of disease severity over the long term. Wen et al. showed that elevation of cord blood IgE levels in mothers during pregnancy is associated with having physician-diagnosed AD in 2-year-old children.⁶¹

Lactate dehydrogenase

Lactate dehydrogenase (LDH) is an enzyme that is present in almost all cell types and is involved in carbohydrate metabolism. LDH is released from damaged cells and is therefore commonly regarded to be a marker of malignancy, cardiac disorders, and hemolysis. Mukai et al. have demonstrated that serum LDH levels are closely correlated with the clinical scores of pediatric and adult AD patients.⁶² A large majority of AD patients who display elevated LDH levels (higher than 300 IU/L) before treatment suffer more severe skin eruptions. In a meta-analysis of longitudinal studies, Thijs et al. showed that the serum LDH level is a good marker of disease severity in AD.⁵⁹

Vitamin D

Vitamin D has immunomodulatory effects.⁶³ Several studies have shown that patients affected by mild AD exhibit higher serum vitamin D levels than those with moderate or severe AD,^{64,65} suggesting that vitamin D deficiency is associated with the severity of AD. On the other hand, Bäck et al. reported that higher vitamin D intake during the first year of life is correlated with an increased risk of eczema at age 6.⁶⁶ However, Chiu et al. did not find any correlation between vitamin D levels and disease severity in AD.⁶⁷ The effects of vitamin D on the pathogenesis of AD might depend on the patient's characteristics and condition. Further studies about the relationships between vitamin D and AD might be necessary.

Cellular biomarkers

Eosinophils

Blood eosinophilia is seen in most AD patients and is correlated with disease severity.⁶⁸ However, some AD patients display normal blood eosinophil counts in spite of disease activity. Therefore, the determination of eosinophil numbers in blood is not a reliable method for establishing a diagnosis of AD. In addition to eosinophils, eosinophil-derived products are present in increased amounts in the circulating blood and inflamed skin of AD patients. The serum level of eosinophil cationic protein is regarded as a biomarker of disease severity.^{69,70}

Platelets

Platelets are important for the development of inflammation, in addition to their functions in hemostasis and thrombosis.^{71–74} The mean platelet volume is often used as an inflammatory marker in several diseases. Pediatric AD patients demonstrate higher mean platelet volumes than healthy subjects.⁷⁵ Interestingly, Fujisawa et al. showed that platelets from adult patients with AD contain high levels of TARC and release a considerable amount of TARC,⁷⁶ suggesting that platelets are another source of TARC in AD patients. Furthermore, the levels of platelet-derived soluble mediators are higher in adult patients with AD than in healthy subjects and are correlated with disease severity in such patients.^{77,78} However, platelet-related biomarkers were less frequently studied and require further investigation.

TABLE 1. CIRCULATING BIOMARKERS FOR ATOPIC DERMATITIS IN CHILDREN

Type of biomarkers	Purpose	Biomarkers	References
Biomarkers for severity	Measurement of disease severity for a short term	TARC/CCL17 MDC/CCL22/TSLP Soluble E-selectin Soluble CD30 ECP	Nakazato et al. ⁶ Fujisawa et al. ⁷ Leung et al. ¹⁶ Lee et al. ²² Nygaard et al. ²¹ Laan et al. ⁴⁸ Frezzolini et al. ⁵⁴ Halmerbauer et al. ⁷⁰ Pucci et al. ⁶⁹ Fukiwake et al. ⁶¹
	Measurement of disease severity for a long term	Total IgE	
Biomarkers for prognosis	Prediction of disease progression	Total IgE (Cord blood)	Wen et al. ⁶⁰

CCL, C-C motif chemokine ligand; MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin.

Discussion

As described in this review, there have been many reports about biomarkers of AD in children (Table 1). Various types of molecules, such as chemokines, cytokines, and soluble adhesion molecules, can be used as biomarkers of AD. In a study of several soluble biomarkers involving a meta-analysis of both longitudinal and cross-sectional studies, Thijs et al. demonstrated that the serum TARC level is the most reliable biomarker of AD severity.⁵⁹ It is suggested that measurement of serum TARC levels is useful for determination of disease severity, evaluation of treatment efficacy, and understanding of skin conditions by the patients.⁸ Furthermore, meta-analysis of cross-sectional studies reporting serum levels of CTACK, MDC, IL-18, and LDH reveals that these indicators are possible good markers for disease severity.⁵⁹ While many mediators such as chemokines and cytokines are regarded as biomarkers for disease severity in a short period, serum IgE level is thought to be an indicator for disease progression as well as disease severity.⁶⁰

AD is known to be a highly heterogeneous disease. Some patients with severe AD have serum levels of biomarkers such as TARC in the normal range. On the other hand, some patients with mild AD have high levels of them. Therefore, it may not be enough to understand the skin conditions by measuring a single indicator in patients with AD. It has been demonstrated that a combination of serum biomarkers shows a better correlation with disease severity compared with a single biomarker in patients with AD.⁷⁹ These findings suggest that it may be more useful to measure several biomarkers together than a single biomarker.

Elevation of serum IgE levels is found in 80% of AD patients. AD can be categorized into the IgE-high extrinsic type and the IgE-normal intrinsic types.⁸⁰ In extrinsic AD, allergic conditions may be preceded by skin barrier impairment. Protein antigens can penetrate through the disrupted barrier, and epidermal Langerhans cells serve as antigen-presenting cells to Th2 cells. On the other hand, intrinsic AD is immunologically characterized by the higher expression of interferon- γ , and nonprotein antigens, such as metals and haptens, may induce dermatitis in intrinsic AD. Several studies have shown that no significant differences in some serum biomarkers are found between extrinsic-type and intrinsic-type AD.^{22,40}

Thus, several circulating biomarkers for disease severity of AD have been identified. However, some biomarkers such as IL-17, IL-33, and platelet-related indicators have not been studied in sufficient detail. Therefore, additional studies are needed to determine the utility of biomarkers for facilitating the treatment and follow-up of pediatric AD patients. Recently, several targeted biological therapies have demonstrated efficacy in previously resistant inflammatory diseases. In addition to measuring disease severity, some mediators might become therapeutic targets for treating AD in the future.

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Author Disclosure Statement

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Address correspondence to:

Risa Tamagawa-Mineoka, MD, PhD
 Department of Dermatology
 Graduate School of Medical Science
 Kyoto Prefectural University of Medicine
 465 Kajii-cho, Kawaramachi-Hirokoji
 Kamigyo-ku
 Kyoto 602-8566
 Japan

E-mail: risat@koto.kpu-m.ac.jp

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