**Moderate to Severe Atopic Dermatitis in Children;** Focusing on Th2 Cytokine Receptor Antagonists and Janus Kinase Inhibitors

**Abstract**

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, and a life-long disease with marked impairment in quality of life. AD is considered a starting point of ‘atopic march’, which begins at a young age and may progress to systemic allergic diseases. In addition, it is strongly associated with comorbid allergic diseases and other inflammatory diseases, such as arthritis and inflammatory bowel disease.

Understanding the cause and pathogenesis of AD is essential for developing targeted therapy. Epidermal barrier dysfunction, immune deviation towards a T helper 2 pro-inflammatory profiles, and microbiome dysbiosis play important roles in AD. The systemic involvement of type 2 inflammation, whether acute or chronic, extrinsic or intrinsic is obvious in any type of AD. Studies on AD endotypes with unique biological mechanisms have been conducted according to clinical phenotypes such as race or age, but endo-phenotypes are not clearly defined yet. Therefore, AD is still being treated according to guidelines based on severity, rather than targeted therapy by endotype.

Infancy-onset and severe AD are known risk factors leading to the atopic march. In addition, up to 40% of infancy-onset AD persists chronically into adulthood, and is more often accompanied by other allergic diseases. Therefore, early intervention strategies to identify these high-risk infants and young children and to repair impaired skin barrier as well as to control systemic inflammation may improve long-term outcomes in patients with AD. However, to the best of our knowledge, there is no study evaluating the effect of systemic therapy in high-risk infants for early intervention on atopic march.

This is a narrative review that addresses the latest knowledge of moderate to severe AD in children with a focus on systemic treatment, including Th2 cytokine receptor antagonists and Janus kinase inhibitors.

**Keywords;** Atopic dermatitis, Eczema, Child, Etiology, Therapeutics, Biological products
**Key message**

The pathophysiology of AD is characterized by strong Th2 response, although the extent of Th22, Th17/IL-23 and Th1 responses varies with disease subtype.

Children with moderate to severe AD require appropriate early systemic therapy to reduce systemic inflammation with increased Th2 cytokines.

Currently, dupilumab, which blocks the IL-4/IL-13 receptors, has equivalent efficacy in both extrinsic and intrinsic AD with a favorable safety profile from the age of 6 months.

**Introduction**

Atopic dermatitis (AD) is a highly heterogeneous chronic inflammatory skin disease. AD was once considered an early-onset pediatric disease that mostly resolves around the age of 2 to 3 years.1 Although, approximately 40%-60% of infancy-onset AD shows remission by the age of 6 to 7 years, recent studies have found that AD is a life-long disease with recurrent exacerbations.2,3,4 AD frequently accompanied by systemic allergic diseases, other inflammatory diseases, as well as psychosocial disorders such as depression, anxiety, sleep disorders, and attention deficit hyperactivity disorder, and so the disease burden is high.5,6

Given the fact that 85% of all AD patients begin before the age of 5 years, this period is not only important for the development of AD, but may also be very essential for modifying the disease course.

Recent studies have provided new insights into the complex pathophysiology and various phenotypes of AD. In addition, new agents are being tried for patients with moderate to severe AD based on an extended understanding of the pathogenesis.

This review describes the latest knowledge about AD in children. We tried to address why early appropriate treatment is important for young children with AD. We also review its pathogenesis and various phenotypes, and currently available systemic therapeutics for children with moderate to severe AD who do not respond to topical treatment.
Atopic march begins with atopic dermatitis

The “atopic march” is the progression of allergic diseases from AD to the other immunoglobulin E (IgE)-mediated diseases such as food allergy (FA), allergic rhinitis and asthma. Over the past 20 years, the term ‘atopic march’ has been widely used to describe changes in the temporal prevalence of allergic diseases reported in epidemiological studies; from AD and FA in infancy to allergic rhinitis and asthma in childhood. These results led to the hypothesis that AD is the first manifestation of an atopic phenotype that begins in early infancy. There is epidemiological and experimental evidence supporting AD as the first initiation of allergic diseases. Several prospective birth cohorts have shown an association between early-onset AD and the development of asthma and allergic rhinitis later at school age. The risks of respiratory allergic diseases are greater in children with the early-onset persistent AD phenotype. Patients with AD who have specific IgE antibodies (extrinsic AD) by the age of 2 to 4 years are at higher risk for progressing atopic march to allergic rhinitis and asthma than those who have not (intrinsic AD). The Canadian birth cohort study found that a significantly increased risk of food allergy, asthma and allergic rhinitis was observed in children with AD and allergic sensitization at age 1 year compared to non-sensitized children without AD. A defective skin barrier, a hallmark of AD, is suggested as one of the mechanisms of atopic march.

A recent systematic review and meta-analysis of 7 birth cohort studies evaluated AD prevalence across 3 to 6 time points, ranging from 3 months to 26 years of age and has found no significant difference in AD prevalence before and after childhood. The presence of AD symptoms was variable. Individuals reported intermittent periods without symptoms followed by periods with symptoms again. The reason for similar estimated prevalence across age time points is due to the combination of the 3 categories; active disease in both childhood and early adulthood, intermittent clearance periods of disease, and later onset disease.

A study with 2 population-based birth cohort studies has shown that only a small proportion of children with AD (~7%) follow the complete manifestations of the atopic march. However, several studies have found that individuals with early-onset AD are more likely to have symptoms later in life, and approximately 17%-31% of patients who developed AD by the age of 2 years had AD present at all-time points up to the age of 18 years. Approximately 40% of adults with AD
is the infancy-onset type; 30% have chronic symptoms into adulthood (early-onset persistent phenotype), and 10% have intermittent periods of symptoms (early-onset intermittent phenotype). Therefore, it is important to identify infants at high-risk for AD that will persist into childhood and adolescence. Then, early intervention is required to modify the atopic march for them. (See graphical abstract) However, to date, there has been no intervention study for modifying atopic march in infants with moderate-to-severe AD.

**Pathogenesis**

The pathophysiology of AD is complex and multifactorial, caused by interactions between various factors including epidermal barrier dysfunction, immune dysregulation, microbiome dysbiosis and pruritus, with strong genetic susceptibility. Understanding the pathogenesis of AD is essential for developing and targeting therapies. A considerable body of evidence suggests that both epidermal barrier dysfunction and immune deviation to T helper 2 (Th2) pro-inflammatory profile play key roles in AD.

The 2 different hypotheses have been proposed: inside to outside and outside to inside. The first is the hypothesis that abnormalities start with the innate immune system, causing skin inflammation, which leads to barrier impairment when stimulated by antigens or irritants. Various mutations and polymorphisms of inflammatory genes have been associated with AD, e.g., interleukin (IL) 4 receptor α and the cluster of differentiation (CD)14 genes, the serine protease inhibitor Kazal type 5 (SPINK5), Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), IL-4, and IL-13. Th2 lymphocyte-dominant immune dysregulation produces IL-4 and IL-13, which inhibit expression of filaggrin (FLG).

The outside-in hypothesis suggests that the impaired skin barrier is the first step in AD pathogenesis and causes immune dysregulation. FLG is an important structural protein of the stratum corneum (SC) for proper epidermal differentiation and skin barrier function. FLG breakdown products, produced in the cornified layer, contribute to maintaining skin moisture, pH regulation, barrier permeability, and microbial protection. The FLG loss-of-function mutation and its effects on epidermal integrity provided strong evidence with the outside-in hypothesis. Although there has been still debate about which comes first, epidermal barrier dysfunction and
immune dysregulation play a major role in the pathogenesis of AD as they interact closely with each other.

Recently, it has been suggested that the barrier-initiated pathogenesis of AD may induce immune dysregulation, which could further compromise permeability barrier function, forming a potential outside-inside-outside vicious circle in AD.

Although AD is still characterized by a well-known strong Th2 immune responses, it has recently been recognized as a more heterogeneous disease with additional involvement of Th22, Th17/IL-23 and Th1 cytokine pathways depending on the disease subtype.\(^2\)

The epidermal barrier is composed of the SC, which constitutes corneocytes and the extracellular matrix, so called “bricks and mortar structure” and tight junctions (TJs). Intact skin is important as a physical and immunological barrier against allergens, microbes and chemicals. Skin barrier impairment, caused by inherited defects or acquired insults, is characterized by downregulated epidermal barrier structural proteins (including FLG, keratins, loricrin, involucrin, and cell adhesion molecules), decreased intercellular lipid and enzymes, decreased antimicrobial peptide(AMP)s, increased skin pH, and reduced skin microbiome diversity with a greater abundance of *Staphylococcus aureus*.\(^2\) The majority of patients with AD have a reduction in epidermal terminal differentiation and SC ceramide levels, either primarily or secondarily by immune-mediated mechanism. The disrupted epithelium exposed to stimuli such as proteolytic allergens, bacteria, parasites, and chemicals promotes antigen penetration and triggers a variety of proteinase-activated receptors and pattern recognition receptors on barrier epithelial cells, inducing the release of epithelial-derived cytokines (alarmins) such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. In epithelial regulation of allergic-type 2 responses, 3 epithelial-derived cytokines of TSLP, IL-33, and IL-25 are critical mediators of type 2 inflammation through activation of dendritic cells (DCs) and type 2 innate lymphoid cells (ILC2s). DCs present at barrier surfaces capture and present processed allergens to naive T cells in the draining lymph nodes through MHC class II molecules. In the presence of IL-4, naive T cells differentiate into Th2 cells. Th2 cell is the major cell type that skews immune reaction towards allergy by producing cytokines IL-4, IL-5, IL-9, IL-13, and IL-31. Activated Th2 cells and ILC2s release IL-4 and IL-13, which promote immunoglobulin E (IgE) class switching.\(^1,2,19-23\) In addition, IL-4 and IL-13 stimulate keratinocytes to produce TSLP. The overexpression of TSLP in the keratinocytes of both acute
and chronic lesions was identified in AD. TSLP activates OX40 ligand-expressing dermal DCs to induce naïve T cells into inflammatory Th2 cells. The epidermal production of TSLP is correlated with the clinically observed lesions, severity, and persistence of AD.

Cytokines and chemokines, such as IL-4, IL-5, IL-13, eotaxins, CC chemokine ligand (CCL)17, CCL18, and CCL22, are produced by Th2 cells and DCs and stimulate the infiltration of DCs, mast cells, and eosinophils into the skin. ILC2s are a potent source of IL-5 and IL-13.

IL-22, an α-helical cytokine of the IL-20 subfamily and strongly upregulated in AD, is produced by the Th22 cell subset. IL-22 signals via a heterodimer of IL-22 receptor 1 (IL-22R1) and the IL-10 receptor 2 (IL-10R2), which are expressed on epithelial cells in the skin (keratinocytes), lung and gut. Increased level of IL-22 acts as a pro-inflammatory cytokine, leading to upregulation of antimicrobial peptides in synergy with IL-17. IL-22 has also been suggested to induce epidermal hyperplasia by promoting keratinocyte proliferation and barrier defects through inhibition of terminal differentiation. IL-22 plays important pathogenic roles in the initiation and development of AD and is correlated with AD severity.

Th1 and Th17 cells have been suggested to play some roles, especially in certain subtypes, such as intrinsic, pediatric, and Asian phenotype. However, Th2 and Th22 cells play predominant roles in all subtypes of AD. Dupilumab, which blocks IL-4/IL-13 receptors, has equivalent efficacy in both extrinsic and intrinsic AD, as well as in pediatric and adult AD. Similar or higher Th2 and Th1 activity, but much greater Th22 and Th17 immune responses are seen in the lesional skin of patients with intrinsic AD than in those with extrinsic AD.

Itch is identified as the most burdensome symptom in AD, leading to unremitting scratching, further damaging the epithelial barrier and impairing the quality of life of patients and their family members including caregivers. Itch is primarily a sensory perception of the skin, mediated by unmyelinated C-fibers and thinly myelinated Aδ fibers originated from cell bodies in the dorsal root ganglion. It has been suggested that endogenous and exogenous pruritogens such as histamine, 5-hydroxytryptamine, proteases, substance P, various cytokines including IL-31 and TSLP, and environmental allergens can signal through specific itch pathways on nerve fiber endings. IL-31 is a potent pruritogenic cytokine in AD. Physical damage due to chronic scratching significantly increases cutaneous TSLP levels. TSLP causes pruritus directly as a pruritogen and indirectly as inducing Th2 related cytokines that activate sensory neurons. In
addition, IL-4 is known to enhance neuronal responsiveness to multiple pruritogens. Therefore, pruritogens including TSLP and Th2 cytokines are implicated in AD development and aggravation by inducing itching, scratching and skin barrier dysfunction.²⁴

Recently, there is growing evidence for an important role of the microbiome in the pathogenesis of AD; abundance of *S aureus* and relative reduction of commensal organisms, which may play a role in regulating *S aureus* growth.³²

**Subtype**

AD is a heterogeneous disease with several phenotypes and endotypes, which are characterized by the activation of diverse cytokine signaling pathways, involving Th1, Th2, Th22, and Th17 cells, depending on the disease subtype. Phenotypes can be classified according to clinical features such as age, severity, race, therapeutic response, etc. An endotype is a subtype of a health condition, which is defined by a distinct functional or pathobiological mechanisms, such as extrinsic/intrinsic AD based on atopic status. Endo-phenotype is a term for connecting clinical phenotype and mechanical endotype. Defining distinct endo-phenotypes is one of the key elements in determining personalized therapy. If there is a unique cytokine signature that characterizes individual endotypes, personalized therapy can be possible. Studies on the endo-phenotype based on race/ethnicity have been conducted, but defining them requires further research with sufficient subjects. In order to clarify the subtype of the endo-phenotypes for race/ethnicity, additional studies with more sufficient subjects are needed. Here, we describe the subtypes based on age of onset, atopic status and disease chronicity, which have shown several distinct characteristics.

1) **Subtypes based on the age of onset**

The clinical phenotypes of AD according to the age of onset can be defined clearly. Generally, 4 types have been classified for children and adolescents: infantile (under 2 years), early childhood (between 2 and 6 years) late childhood (between 6 and 12 years), adolescent (between 12 and 18 years).³³,³⁴

A European birth cohort study revealed that the prevalence of asthma and FA by 6 years of age was strongly increased among children with early phenotypes (within age 2 years) of AD, especially with persistent symptoms.³⁵ Similarly, a recent study in Korean school-aged children and adolescents with AD found that the patients with infancy-onset (< 2 years of age) showed
more comorbid allergic diseases of FA, allergic rhinitis and asthma as well as inhalant allergen sensitization than those with later onset (preschool- and childhood-onset). Therefore, while a significant proportion of patients with early onset phenotype can go into complete remission before age 2 years, another proportion, estimated at up to 40%, continues to suffer from the disease over a longer period of time, and patients in this category may represent a population at high risk for atopic march.

Since the immune system changes with age, AD across different age groups may present diverse phenotypes and endotypes. Unique cytokine signatures characterizing individual pediatric endotypes may enable age-specific tailored treatment.

Shape and distribution of AD lesions vary with age groups; cheek, scalp, and trunk in infants, extensors of limbs in younger children, flexural distribution of limbs in older children, and additional lichenified lesions of forehead and neck in adolescents. These changes might derive from background endotype skewing over time. Therefore, it is crucial to define those changes for proper treatments.

In addition, even in children, there may be differences in the underlying immunological profiles depending on the atopic status (intrinsic vs extrinsic), disease duration (acute vs chronic), severity (mild vs moderate to severe) as well as race. However, unlike adults, the distinction between extrinsic and intrinsic may not be clear in infants and young children, because some with intrinsic AD evolve into an extrinsic type through sensitization.

Studies with peripheral blood suggest that infants present overexpression of regulatory T cells and a greater Th17 lineage capacity versus adults. At birth, immune responses are Th2 biased, with low Th1/interferon gamma levels in healthy newborns and those who will have AD. The cutaneous lymphocyte antigen (CLA)+ Th1 cells were lower in infants and increase with age. Children (<5 years) with moderate-to-severe AD show a suppressed and delayed development of skin-homing (CLA+) Th1 cells in the peripheral blood. Levels of CLA+ Th1 cells in infants with AD were the lowest compared to both age-matched controls and older children with AD. However, frequencies of CLA+Th2 cells were similarly expanded across all ages of infants, children, adolescents, and adults with AD and are significantly higher than in age-matched controls, even in infants. After infancy, CLA−Th2 frequencies were increased in AD of all age groups,
suggesting systemic immune activation with disease chronicity. In addition, IL-22 frequencies also increased from normal levels in infants to significantly higher levels in adolescents with AD compared to their respective control subjects. Principal components analysis of the flow cytometric marker frequencies (percentages) in patients with AD across ages have shown 3 meaningful age clusters of infants (0-5 years), children and adolescents (6-17 years) and adults (≥18 years), suggesting unique molecular profiles of AD according to age.

The epidermal hyperplasia was greater in the lesional skin of children younger than 5 years of age with onset of AD within 6 months than in those of adults. In addition, the nonlesional skin of infants and young children also showed significant hyperplasia to levels as high in nonlesional skin of adults. Epidermal TSLP expression as early as age 2 months is associated with AD later in life. Taken together, true AD can be initiated before the lesional skin appear in children with early AD.

A study using skin from moderate to severe AD of different age groups (0-5, 6-11, 12-17, and ≥18 years) have found that the skin of all AD age groups expressed common features of Th2 (Th2-related markers of IL-13, CCL17/TARC, CCL18/PARC, and IL-4R) and Th22 skewing (Th22-related markers of IL22 and S100As) compared to those of age-matched controls. The differences in expression levels of cytokines between age groups of AD include; infants showed the greatest Th17-related cytokines, whereas long-standing adults displayed Th1 skewing cytokines including IFN-γ and CXCL9/CXCL10/CXCL11, suggesting disease chronicity. The expression levels in Th17-related genes were inversely related to developmental age in children aged 0 to 11 years with or without AD, and were generally higher in skin of AD than in that of healthy controls, and presented a 2-peak, with the highest in infants, followed by adults. Although the role of Th17 in AD has not yet been clearly elucidated, IL-17 in AD is not as important as in psoriasis.

Table 1. Phenotypes of atopic dermatitis by the age of onset

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Infancy</th>
<th>early childhood</th>
<th>late childhood</th>
<th>adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age</td>
<td>&lt; 2 years</td>
<td>2≤age&lt;6</td>
<td>12≤age&lt;6</td>
<td>12≤age&lt;18</td>
</tr>
</tbody>
</table>
2) **Subtypes based on atopic status**

AD has long been subdivided into 2 subtypes: extrinsic/atopic and intrinsic/non-atopic subgroups. The extrinsic phenotype (60%-80%) is characterized by high serum total and specific IgE levels, eosinophilia, personal and family atopic background, and a greater rate of FLG mutation. In contrast, the patients with intrinsic AD (20%-40%) have normal IgE levels, no other atopic background, female predominance, delayed disease onset, and preserved barrier function.\(^{44,45}\)
However, even in the same extrinsic subtype, there are differences in the sensitized allergens as well as stage and site of AD lesions according to age. Sensitization to food allergen is common in infants and young children, whereas sensitization to inhaled allergen is more frequent in older children.

Most of the studies in infants and young children tried to characterize disease phenotype with peripheral blood. The eosinophil count, ECP level and detection rate of IL-5 were higher in infants with extrinsic AD than in those with intrinsic AD. \(^{46}\)

Increased Th1 signal (IFN-γ, CXCL9, CXCL10, and MX-1) and more pronounced Th17/Th22 activation (IL-17A, CCL20, Elafin, and IL-22), which are known to be linked to psoriasis were significantly greater in intrinsic AD. Levels for antimicrobial activity (S100A9 and S100A12), which are co-regulated by IL-17/IL-22, are greater in intrinsic versus extrinsic lesions. \(^{47}\)

In the skin, Th1/interferon-related gene expression and levels of the Th17 chemokine CCL20 correlated with disease severity in patients with intrinsic AD, whereas Th2 markers correlated positively with disease severity and negatively with barrier products of loricrin, periplakin, and FLG in patients with extrinsic AD. \(^{46}\) Intrinsic AD has the inflammatory (IL-22, IL-36α/γ, IL-36RN, and CCL22) and lipid metabolism pathways that overlap with psoriasis, supporting Th17/IL-23 and IL-22 as common profiles of the 2 conditions. \(^{47}\)

Although each type has characteristic cytokine profiles, both 2 types have a similar clinical presentation in the lesional skin and show a similar increase in Th2 marker. The lesional and nonlesional skin from both extrinsic and intrinsic AD showed increased infiltration of T-cells and DCs along with epidermal hyperplasia in the lesional skin compared to the nonlesional skin; however, greater cellular infiltrates (T cells, myeloid DCs, and Langerhans cells) were observed in intrinsic AD. \(^{47}\)

Table 2. Phenotypes of atopic dermatitis by atopic status

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Extrinsic</th>
<th>Intrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>high</td>
<td>Normal</td>
</tr>
<tr>
<td>Specific IgE</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>
3) Subtypes based on stage

The skin lesions vary greatly, but can be classified as acute or chronic. Acute lesions begin with erythematous papules and serous exudates and include secondary lesions such as excoriations and crusted erosions due to scratching. When the acute lesions persist, subacute lesions such as erythematous scaly papules and plaques appear. If the itch and rash progress, chronic lichenified lesions featuring accentuated skin markings with hyperpigmentation or hypopigmentation develop.

AD presents with various lesions in different stages; it is common to find both acute and chronic lesions in the same patients, and both lesions often overlap in the same areas. Acute lesions begin with a marked increase in AMP levels and the upregulation of Th2 and Th22 cytokines as well as lesser increase of IL-17 levels. The intensification of the Th2 and Th22 cytokine axes with disease chronicity has been demonstrated, with significant increases in Th1 and Th17.\textsuperscript{48,49} Taken together, acute inflammation in AD is driven by type 2 cytokines, while immunological mechanisms in the chronic stage are associated with enhanced Th2 and Th22 as well as additional Th1 and Th17 responses; changes from acute to chronic AD are quantitative rather than qualitative in terms of shifts in Th2, Th22, Th1 and Th17 responses, with additional features developing only in chronic inflammation.\textsuperscript{48,49}

Table 3. Phenotypes of atopic dermatitis by stage

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Erythematous papules and vesicles, oozing</td>
<td>Scaly patches and plaques, lichenification, nodules within plaques,</td>
</tr>
</tbody>
</table>
**Prevention of AD through epithelial barrier enhancement**

Recent evidence suggests that skin barrier defects are one of the key initiators of allergic march, from AD to FA, allergic rhinitis and asthma. Allergen penetration through the defective skin barrier can lead to transcutaneous sensitization. That is why there are studies on moisturizers for preventing AD in infants at risk by enhancing epithelial barrier function.

However, there are mixed results of studies on emollients for AD prevention. The 2 well-designed studies have shown promising results for the role of emollients in preventing AD.\(^50,51\) However, recent studies including the barrier enhancement for eczema prevention (BEEP) study and the prevent infant atopic dermatitis (PreventADALL) study have shown that no preventive effect of emollients on the AD or FA development in high-risk infants.\(^52,53\) A large randomized controlled study of high-risk infants (n= 1394) did not support that daily application of emollients during the first year of life prevent AD, FA, sensitization, and allergic rhinitis.\(^53\)
In addition, there are conflicting results on the relationship between the use of moisturizers and food sensitization. The Prevention of Eczema By a Barrier Lipid Equilibrium Strategy (PEBBLES) pilot study in 2018 found that applying emollient in high-risk infants demonstrated a non-significant trend in reducing food sensitization at 6 and 12 months of age, with non-significant trend towards a reduction in AD at 12 months. However, per protocol analysis (only including infants who received ≥ 5 days/week of study treatment) revealed a significant reduction in food sensitization at 12 months in the treatment group. A recent study has shown the negative effects of emollients on allergen sensitization. The Enquiring About Tolerance (EAT) study showed dose-response relationships between moisturizer frequency and the development of both food and aeroallergen sensitization at 36 months. However, this is not a true prospective study; at 3 months of enrollment, families completed a questionnaire that included questions about the frequency and type of moisturizer applied and parental report of dry skin/eczema, and researchers found a positive association between moisturization frequency at 3 months of age and the development of FA and sensitization at 3 years of age. The emollients used in the studies including EAT study were greatly varied, and the ingredients (substances of actives and excipients) of them were widely different such as vegetable oils/creams, petrolatum-based lotions, and trilipid creams with ceramide. Obviously, some formulations can deteriorate the skin condition and induce contact dermatitis, further sensitization to allergens, whereas others such as trilipid cream, which are similar to skin lipids, improve the skin barrier function. Several clinical studies have shown that ceramide-dominant emollients have additional beneficial effects not only on dry skin but also on AD treatment. The emollients used in the BEEP and PreventADALL studies were petrolatum based, which are thought to be less effective than trilipid emollients in reducing TEWL. As expected, the pilot study using a trilipid emollient (n=77) showed a trend to reduce the risk of AD and food sensitization in infants at 6 months and 12 months. As a follow-up to this pilot study, a large randomized controlled trial is currently underway to determine whether routine prophylactic use of ceramide-dominant emollients can prevent the onset of AD and the subsequent allergic march.

The frequency and site of application varied; from 4 times a week, once a day, or twice a day, with whole body or primarily on the face (cheeks and perioral area). In order to have optimal effect, emollients, which has a beneficial effect on restoring lipid abnormalities, need to be tailored up to 80% of the disease cases begin in infancy were the subjects’ characteristics, which could
explain the discrepancy between the study results. Some included infants from the general population, while others selected a population at high risk for AD.\textsuperscript{52,57}

Taken together, careful interpretation of the studies on the effects of moisturizer for prevention of AD or FA is required since differences in clinical study design including type of moisturizers may lead to discrepancies in the outcome of studies. Although additional researches are needed to evaluate the efficacy of moisturizers depending on their formulations, efforts to enhance epithelial barrier are necessary for high risk children.

**Treatment:**
Most patients with mild to moderate AD respond to standard topical anti-inflammatory therapies with optimized skincare. Nevertheless, pediatric patients with moderate to severe AD are often not adequately controlled by avoidance of irritants or triggers (food and environment), application of emollients, and intensive topical treatments. The importance of treating AD in pediatrics comes from the fact that up to 80\% of the disease cases begin in infancy or early childhood and AD is the early presentation of the allergic march. Therefore, it is ideal for the target of treatment to shift from resolving the symptoms to controlling the immune reaction behind it. This is why systemic treatment of AD in young children is necessary. However, treatment options at this age are limited; there is a lack of data on the clinical trials and long-term safety of new agents. In addition, there are no clinical studies to determine if the early systemic treatment of immune dysregulation can modify the disease course in infants and early children. Here is a narrative review of new, currently accepted systemic therapies, Th2 cytokine receptor antagonists and Janus kinase inhibitors (JAKi), for children with moderate to severe AD.

1) **Th2 cytokines receptor antagonists:**
A Th2 immune response is considered the core pathway leading to cutaneous inflammation in AD. IL-4, IL-13 and IL-5 or their respective receptors are the focus of drug development strategies that aim to modulate the Th2 response.\textsuperscript{59,60} In addition, IL-4 and IL-13 receptors are expressed on neurons and are believed to play additional roles in the itch-scratch mechanism.\textsuperscript{61} Dupilumab, lebrikizumab, tralokinumab, and nemolizumab are examples of targeted biologics that specifically focus on distinct immune pathway and their cytokines/receptors.
**IL 13 / IL 4 antagonists:**

**Dupilumab** is a fully human monoclonal antibody that inhibits downstream signaling of both IL-4 and IL-13 by binding to IL4Rα. IL-4 and IL-13 share a heterodimeric receptor composed of IL-4Rα and IL-13Rα1, known as the type 2 receptor of IL-4. It is approved for the treatment of moderate to severe AD administered subcutaneously in pediatric age from the age of 6 months and for atopic comorbidities such as allergic asthma and nasal polyposis, conferring its broad therapeutic profile. Four phase 3 studies evaluated the efficacy and safety of dupilumab in treating moderate to severe AD in pediatrics age form 6 months to 17 years. (Table 4) (Figure 3,4)

In adolescent, 200 or 300 mg dupilumab every 2 weeks or 300 mg dupilumab every 4 weeks were administered for 16 weeks. The improvement in eczema area and severity index (EASI) score in dupilumab 2-week and 4-week regimens versus placebo was -65.9 % and -64.8%, respectively. In children aged 6 years to 11 years, a weight-based regimen of dupilumab dosing of 100/200 mg every 2 weeks or 300 mg every 4 weeks for 16 weeks, in combination with a medium potency TCS resulted in an improvement in EASI score of dupilumab versus placebo was -82% and -78% respectively. (Table 1) (Figure 3,4)

Results of these clinical trials revealed that dupilumab is associated with an increased incidence of conjunctivitis. This adverse reaction of special interest was described to be mild to moderate and resolved by the continuation of treatment. Interestingly, it was found to occur in patients with AD alone rather than those with comorbidities such as asthma, chronic rhinosinusitis with nasal polyps, or eosinophilic esophagitis; however, the exact pathophysiology behind it remains unclear. In the real world studies in children, dupilumab associated conjunctivitis has also been reported, however, fewer than in those of adults. Similar results were detected in younger age groups (6 months to 6 years) who were given 200 or 300 mg of dupilumab every 4 weeks for 16 weeks in combination with TCS. The degree of improvement in EASI score reached -70%, and conjunctivitis was the most frequently detected Treatment Emergent Adverse Event (TEAE). Results from 28 weeks extension to be published. (Table 1) (Figure 4)

An open-label phase 3 study was extended for 52 weeks to evaluate the efficacy and long-term safety of dupilumab with concomitant topical therapy in children aged 6 to 12 years. Weight-
based regimens, either 2 mg/kg or 4 mg/kg of dupilumab on weekly basis provided percent change in EASI from baseline to week 52 by -92% and -84%, respectively. Nearly all children reported at least one TEAE which were mild to moderate with a tendency to be dose related; none led to treatment discontuation.69 (Table 1) (Figure 4) In summary, dupilumab has a favorable safety profile and can be administered for long-term treatment in pediatric AD.

**IL-13 selective antagonist:**

Selective antagonist of IL-13 has been proposed to manage AD and improve the quality of life in patients; therefore, new targeted biologics such as lebrikizumab and tralokinumab have been developed.70 Both agents differ in their binding epitopes and their ability to block one or both receptors of IL-13; lebrikizumab does not block 13α2 receptor chains, whereas tralokinumab blocks binding of IL-13 to both IL-13Rα1 and IL-13α2 receptor chains, the decoy receptor, which may be involved in endogenous IL-13 regulation.70

**Tralokinumab** is a fully humanized antibody targeting IL-13 that blocks its binding to both IL-13Rα1 and IL-13α2 receptor chains.71,72 It has been approved for the treatment of moderate to severe AD in adults after being studied up to 52 weeks as phase 3 studies.73,74 Patients achieved significant improvements in Investigator's Global Assessment (IGA) scores, pruritus, sleep interference, and quality of life and maintained these improvements over time without requirement for TCS.73,74 Recently, results of a phase 3 trial study for tralokinumab monotherapy in adolescents were released. Tralokinumab was given either 150 or 300 mg; the proportion of patients who achieved EASI 75 (75% reduction in EASI score) was above 25% by the end of initial treatment at week 16 and reached from 44% to 64% by the end of maintenance treatment at week 52 with a favorable safety profile. The most common TEAE during the maintenance and safety follow-up period was upper respiratory tract infection. (NCT03526861). (Table 1) (Figure 3)

**Lebrikizumab** is a fully humanized anti-IL-13 antibody that specifically binds to soluble IL-13, does not block the cytokine binding to the receptor, but instead impairs the heterodimerization of IL-4Rα and IL-13Rα1; thereby, inhibiting signal transduction.71,75 Lebrikizumab plus TCS was suggested to provide some additional benefit compared with TCS alone in a proof-of-concept phase 2 trial in adults.76 At week 12, 82.5% of the lebrikizumab group versus 62.3% of the placebo achieved EASI 50, with similar adverse effects in both groups.76 However, its efficacy as a long
term monotherapy for AD has not yet been confirmed. A focus is now placed on ongoing phase 3 in adolescents (NCT04250350). (Table 1)

The comparison of lebrikizumab and tralokinumab results with those of dupilumab is difficult because no head to head comparative studies have been done and there are no results from a phase 3 lebrikizumab study yet. In adults, the improvement in EASI scores after correction to placebo were similar in dupilumab and lebrikizumab (32%-36% and 37%, respectively) and slightly lower in tralokinumab (12%-22%); this may be attributed to differences in the study designs, but because tralokinumab also blocks receptors involved in the endogenous regulation of IL-13. 70,77

**IL-31 antagonist:**

**Nemolizumab** is a humanized monoclonal antibody against the receptor A of IL-31. IL-31 is a prominent pruritogenic cytokine produced by infiltrating Th2 cells in AD; it correlates with disease severity and has been found to be excessively expressed in skin lesions in AD. 31,78 Therefore, IL-31 and its receptor are the focus of strategies to better control the itch-scratch cycle. 79,80 It is approved for moderate to severe AD in adults and approved in Japan from the age of 13 years. In a phase 3 trial, subjects aged 12 to 18 years with moderate to severe pruritus who showed an inadequate response to topical agents were given subcutaneous 60 mg nemolizumab every 4 weeks with concomitant topical agents. 81 After week 16, the mean percent change in the EASI score was −45.9% with nemolizumab and −33.2% with placebo. 81 Adverse events were generally mild to moderate; however, one of the nemolizumab group discontinued treatment due to AD exacerbation. 81 Although some patients reported exacerbation of AD as an adverse event, those patients had reductions in pruritus as measured by the visual analogue scale.81

In an open label, phase 2 study in patients aged 12 to 17 years with moderate to severe AD, nemolizumab was administered subcutaneously as a 60 mg loading dose, followed by 30 mg every 4 weeks until 12 weeks and followed up 8 weeks more. 82 AD related pro-inflammatory biomarkers changed higher in EASI responders than in EASI non-responders. 80 (Table 1) (Figure 3)

As nemolizumab appears to be a promising agent, larger studies are needed to evaluate its long term efficacy and safety. A phase 2 study is ongoing to evaluate pharmacokinetics, safety and efficacy of nemolizumab for moderate to severe AD in children aged 2 years and older (NCT04921345).
2) Janus kinase inhibitors:

Janus kinases (JAKs) are a group of molecules, composed of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). When a cytokine binds to the intracellular domains of type I or type II cytokine receptor, a conformational change is induced, which activates the JAK tyrosine kinases, resulting in phosphorylation of tyrosine residues in the receptor's intracellular domain. The phosphorylation of receptor subunits allows for the recruitment of signal molecules, including latent cytoplasmic transcription factors such as Signal Transducers and Activator of Transcription (STATs); phosphorylated STATs are activated, dimerized and translocated to the nucleus to regulate target gene expression. In general, all Type I and II receptors rely on JAK1/JAK2 for signal transduction. Depending on the particular receptor, 1 or more other members of the JAK family work together to mediate signal transduction. Therefore, each JAKs is often involved in downstream signaling of multiple cytokine receptors in association with other JAK family members. Although tyrosine kinase 2 can partner with both JAK1 and JAK2, JAK3 is a much less widely expressed JAKs protein and is restricted to receptors containing the common γ chain-containing receptors. (Fig.3)

Janus kinase inhibitors (JAKi) are small molecules, can be administered orally or topically, and are recently introduced in the treatments for AD. Currently, more than 90 JAKi are patented, many of which are in clinical development for various indications such as inflammatory bowel diseases and rheumatoid arthritis. As the receptors for Th2 and Th22 cytokines involve downstream JAKs–STAT signaling, JAKi represent interesting compounds for AD treatment.

JAKi approved for or under clinical development for AD can be classified into three main categories: non-selective JAKi (delgocitinib, cerdulatinib, jaktinib, CEE321); dual inhibitors (baricitinib, ruxolitinib, brepocitinib, ATI-1777); and selective JAK1 inhibitors (upadacitinib, abrocitinib, SHR0302).

Inhibiting JAKs exerts a broad immune-pharmacological impact blocking the signal transduction pathways of multiple cytokines. JAKi block numerous cytokines that are involved in many aspects of host defense, hematopoiesis, metabolism, cell growth, and cell differentiation; therefore, it can have multi-systemic impacts. Its serious adverse effects include infections, anemia, pulmonary embolism, malignancy risk, thromboembolic risk, and elevated serum cholesterol. Nonetheless, the hope of the second generation JAKi with increased selectivity to reduce adverse effects
together with preserve efficacy. Herein, we intended to discuss only orally available JAKi that have been studied for pediatrics age.

**Baricitinib** is a JAK1/2 inhibitor; it is approved for the treatment in adults with moderate to severe AD. In 2 independent phase 3 trials for 16 week, the participants who achieved EASI 75 reached 24.8% with baricitinib monotherapy and 36.6% with TCS.86 The most common adverse events were nasopharyngitis and headache.86 No cardiovascular events, venous thromboembolism, gastrointestinal perforation, significant hematological changes were detected, and unlike selective JAK1 inhibitors, there was no increase in acne incidence.86 In a pooled safety analysis of cumulative data from 8 adult studies (n= 2531), simple viral infection and headache were the most frequently reported TEAE with only 2 venous thrombosis events and 1 death.85 With satisfactory improvement and onset of action together with acceptable safety profile, baricitinib is being studied in children aged 2 to 17 years who have had an inadequate response to topical medications (NCT03952559). (Table 1)

As hematopoiesis signaling of receptors depends crucially on JAK2 homodimers, JAK1 selective inhibitors are suggested as a safer choice that avoids the major JAKi adverse reactions. Upadacitinib and abrocitinib are the second generation JAK1 inhibitors studied in children.

**Upadacitinib** is a selective JAK1 inhibitor approved for the treatment of moderate to severe AD in adults and children from 12 years of age. Three phase 3 trials (Measure up 1, Measure 2, and AD up) evaluated the efficacy of upadacitinib for 16 weeks (15 or 30 mg, once daily) in treatment of patients aged 12 years or older with moderate to severe AD.88,89 Measure up 1 and 2 evaluated upadacitinib as monotherapy while AD up examined it with TCS for all participants. The percentage of participants who achieved EASI 75 in the Measure up 1, Measure up 2, and AD up was satisfactory with the 15 mg dose (69.6%, 60.1% and 65%. respectively) and the 30 mg dose (79.7%, 72.9% and 77%. respectively), and both regimens showed statistically significant improvement by week 2. Adverse reactions detected were mild to moderate in severity, most frequently acne, upper respiratory tract infection, headache, oral herpes, and asymptomatic elevation of plasma creatine phosphokinase. Acne was the most common side effect in the 3 studies; Although it was not serious and did not led to discontinuation, it was higher than what was observed in previous studies in rheumatoid arthritis, which might be due to the relatively younger
age of the AD patients. These results demonstrate the potential for upadacitinib to be used as a monotherapy avoiding the burden of the use of TCS. In addition, the incidence of oral herpes infection was less than 3% with upadacitinib monotherapy, unlike that with TCS combination therapy.

Long-term maintenance of upadacitinib efficacy was demonstrated in a 52 week extension for AD up study. The proportion of patients who experienced EASI 75 was 50.8% and 69.0%, in response to treatment with upadacitinib 15 mg and 30 mg, respectively and no new important safety risks were reported.

A blinded extension for the 3 of studies up to 260 weeks is ongoing to demonstrate the long-term safety of the drug. A study for younger ages is currently recruiting (NCT03646604).

Abrocitinib is a JAK1 selective inhibitor that was approved for the treatment of moderate to severe AD after it has been investigated for the treatment of AD in adolescents and adults. Three phase 3 trials studied the efficacy and safety of once daily 100 mg and 200 mg of abrocitinib for 12 weeks. JADE Mono 1 and 2 studied abrocitinib monotherapy in adolescents and adults (adolescents were 22% and 10% of the study subjects, respectively), while JADE TEEN examined abrocitinib plus topical therapy in adolescents. (Table 1) (Figure 3) With the 100 mg dose, the percentage of participants achieved EASI 75 was 40%, 44.5%, and 68.5%, respectively and with 200 mg dose, it was 63%, 61%, and 72%, respectively. Participants from JADE TEEN and the adolescents in JADE mono 1 and 2 were pooled and further assessed for patient-reported signs and symptoms and a substantial improvement in sleep loss and quality of life were evaluated. The most frequently detected adverse events were nausea, vomiting, abdominal pain, headache, increased blood creatine phosphokinase, and acne. Thrombocytopenia was noticed in the 3 studies but improved with continued treatment except only 1 case required withholding treatment for 8 days.

In terms of serious side effects of JAKi, no thromboembolism or major cardiovascular events were reported, and herpes infections were few and none of them was disseminated. In upadacitinib studies, an elevation of liver enzymes were detected in Measure up1 and 2 upadacitinib groups (1.7% versus 1.1% in placebo), which did not lead to discontinuation of treatment and there was 1 case of non-melanoma cancer reported in the upadacitinib 30 mg plus TCS group on day 45 of AD up study. Integrated analysis of a phase 2b study, 4 phase 3 studies and 1 long-term extension
study was performed to evaluate long-term safety of abrocitinib where only 12.7% of the abrocitinib group were adolescent. Herpes zoster was reported in patients of all ages (from 12 to \( \geq 75 \) years) and was found to be higher in age \( \geq 65 \) years, severe disease at baseline, and higher dose of abrocitinib.

Comparative studies were done between the selective JAKi and dupilumab in adults. Upadacitinib 30 mg and abrocitinib 200 mg were superior to dupilumab 300 mg in terms of onset of itch improvement and EASI 75 at 16 weeks. The adverse effects of the 3 drugs were consistent with the previous studies and were mild to moderate in severity. The risk of adverse events was numerically higher in upadacitinib 30 mg and abrocitinib 200 mg compared to dupilumab 300 mg; however, serious events were comparable to those of dupilumab group.

**Conclusion:**

AD is a heterogeneous systemic inflammatory skin disease associated with immune dysregulation, epithelial barrier dysfunction and enhanced neuronal responsiveness to pruritogens. Although the proportion varies per study, about 60%-80% of AD in adults occurs during the first 2 years, and 85% before 5 years of age. Up to 40% of infancy-onset AD will suffer from disease into adulthood and some of these progress to the atopic march.

In addition to concerns about the chronicity of AD, the systemic inflammatory response with increased Th2-related cytokines as confirmed by a panel of serum biomarkers in moderate to severe AD at a young age indicates the need for appropriate systemic treatment to control systemic inflammation. However, for this very important period of young children, we have limited options for the intervention of the disease. Nevertheless, all efforts must be made to treat AD in high-risk infants and young children. For this purpose, background immune dysregulation and related skin characteristics including clinical features and immunologic profiles in young children with AD should be investigated.
Table 4. Summary of phase 3 studies for the use of systemic biologics and JAKi for AD treatment in pediatrics age:

<table>
<thead>
<tr>
<th>Medication (Mechanism)</th>
<th>Age, years (n)</th>
<th>Study design (Duration, week)</th>
<th>Regimen, mg</th>
<th>Patients achieved EASI 75 (%)</th>
<th>TEAEs higher in treatment groups</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab (IL-4/ IL-13 antagonist)</td>
<td>12-17 (251)</td>
<td>Blinded Monotherapy (16)</td>
<td>q2 wk: 200 mg &lt;60 kg 300 mg ≥60 kg q 4 wk 300 mg</td>
<td>q2 wk, 41.5% q4 wk, 38.1%. placebo 8.2%</td>
<td>≥ 5% of patients: Conjunctivitis, injection site reaction.</td>
<td>65</td>
</tr>
<tr>
<td>6-11 (367)</td>
<td>Blinded Plus TCS (16)</td>
<td>q2 wk: 100 mg &lt; 30 kg 200 mg &gt; 30 kg q4 wk: 300 mg</td>
<td>q2wk, 67.2% q4wk, 69.7% placebo 26.8%</td>
<td>≥ 5% of patients: Conjunctivitis, injection site reaction.</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>6-12 years (33)</td>
<td>Open label extension concomitant topical tx. (52)</td>
<td>qwk: 2 mg/kg 4 mg/kg</td>
<td>At 16 wk: 2 mg: 59% 4 mg: 73% At 52 wk: 2 mg: 94% 4 mg: 75%</td>
<td>Each participant had at least one TEAEs Mild to moderate, dose related Conjunctivitis and herpes viral infection</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>6 months to 6 years (162)</td>
<td>Blinded Plus TCS (16)</td>
<td>q4wk: 200 mg &lt; 15 kg 300 mg ≤ 15 kg</td>
<td>Tx: 53% Placebo 11%</td>
<td>Conjunctivitis and herpes viral infection</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Lebrikizumab (IL-13 antagonist)</td>
<td>12 – 17 (52)</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>NCT04250350</td>
<td></td>
</tr>
<tr>
<td>Tralokinumab (IL-13 antagonist)</td>
<td>12 to 17 (301)</td>
<td>Phase 3 Blinded Monotherapy (16)</td>
<td>q2wk: 150mg 300mg placebo</td>
<td>Initial tx: 150 mg: 28.6% 300 mg: 27.8% Placebo: 6.4%</td>
<td>≥ 5% of patients: Upper respiratory tract infection, injection site reaction.</td>
<td>NCT03526861</td>
</tr>
<tr>
<td>Nemolizumab (IL-31 antagonist)</td>
<td>13-18 (143)</td>
<td>Blinded Concomitent topical tx. (16)</td>
<td>q4 wk: 60 mg</td>
<td>drug 25.9% Placebo 18.1%</td>
<td>≥ 3% of patients: Injection site reaction, abnormal cytokine, increased blood creatine kinase</td>
<td>81</td>
</tr>
<tr>
<td>Baricitinib (JAK 1/2 inhibitor)</td>
<td>2-17 years (16)</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>NCT03952559</td>
<td></td>
</tr>
<tr>
<td>Upadacitinib (JAK 1 inhibitor)</td>
<td>12-75 MeasureUp1 (847)</td>
<td>Blinded Monotherapy (16)</td>
<td>Once daily 15 mg 30 mg</td>
<td>Measure up 1 15 mg 69.6% 30 mg 79.7%</td>
<td>≥ 5% of patients:</td>
<td>88</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Efficacy</td>
<td>Other Adverse Events</td>
<td></td>
<td></td>
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<td>--------------------------------------------------------------------------------------</td>
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<tr>
<td>MeasureUp2 (836)</td>
<td>Placebo</td>
<td>Placebo 16.3%</td>
<td>Acne, upper respiratory tract infection, headache, increased plasma creatine phosphokinase</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>12-75 AD Up (901)</td>
<td>Once daily</td>
<td>15 mg: 65% 30 mg: 77% Placebo: 26%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blinded Plus TCS (16)</td>
<td>15 mg: 65% 30 mg: 77% Placebo: 26%</td>
<td>≥ 5% of patients Acne, oral herpes, increased blood creatine phosphokinase.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Abrocitinib (JAK 1 inhibitor)</td>
<td>12-17 (285)</td>
<td>Once daily</td>
<td>15 mg: 65% 30 mg: 77% Placebo: 26%</td>
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</tr>
<tr>
<td></td>
<td>12 to ≥ 65* (387)</td>
<td>100 mg: 40% 200 mg: 63% Placebo: 12%</td>
<td>≥ 3% of patients: GIT upset†, headache.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Blinded Monotherapy (12)</td>
<td>100 mg: 44.5% 200 mg: 61.0% Placebo: 10.4%</td>
<td>≥ 3% of patients: GIT upset†, acne, headache, increased blood creatine phosphokinase, thrombocytopenia.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 to ≥ 65* (391)</td>
<td>100 mg: 68.5% 200 mg: 72.0% Placebo: 41.5%</td>
<td>≥ 3% treatment of patients: GIT upset†, acne, increased blood creatine phosphokinase.</td>
<td></td>
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</tr>
</tbody>
</table>

EASI 75; 75% reduction in Eczema Area and Severity Index, Wk; week, tx; treatment, TEAE; Treatment Emergent Adverse Event, TCS; topical corticosteroid, AD; atopic dermatitis, AESI; Adverse Event of Special Interest, GIT; gastrointestinal tract.

* no upper limit for the age

†GIT upset included nausea, vomiting, and upper abdominal pain
**Figure legend**

**Figure 1: Abstracted Figure**
Subtypes of adults with atopic dermatitis. Approximately 40%-60% of adults with atopic dermatitis are characterized by an early infancy-onset and chronic persisting course into adulthood. At birth, low levels of gamma interferon and increased level of type 2 cytokine producing cord blood T are subsequently associated with infancy-onset atopic dermatitis. Early onset atopic dermatitis and allergic sensitization at early age are at increased risk of early onset persistent phenotype. Among infants of early onset atopic dermatitis, some develop systemic allergic disease such as food allergy, allergic rhinitis, and asthma. Childhood onset and adolescent onset AD account for 10% each. The figure is based on the findings described by reference 8-13, 15, and 16.

**Figure 2. Pathophysiology of atopic dermatitis**
The pathophysiology of atopic dermatitis is complex and multifactorial, caused by the interaction among epidermal barrier dysfunction, immune dysregulation, itch, and microbiome dysbiosis. Impaired epidermal barrier is characterized by downregulated epidermal barrier structural proteins, intercellular lipid and enzymes, decreased AMPs, increased skin pH, and reduced skin microbiome diversity with a greater abundance of *Staphylococcus aureus*. As a results, antigens can be easily penetrated and transepidermal water loss is increased as well as epithelial-derived cytokines (alarmins) such as TSLP, IL-33, and IL-25 are released. Epithelial-derived cytokines are critical mediators of type 2 inflammation through activation of DCs and ILC2s. TSLP activates OX40 ligand-expressing dermal DCs to induce naive T cells into inflammatory Th2 cells, which produce IL-4,5,13, and 31.

Th2 cytokines including IL-31 and TSLP are potent pruritogens. Th2 and Th22 cells play a major role in AD, and Th1 and Th17 cells are suggested to play some roles as well.

Ag, antigen; TEWL, tranepidermal water loss; AMPs, antimicrobial peptides ; TSLP, thymic stromal lymphopoietin, DC, dendritic cell; ILC2, Type 2 innate lymphoid cells
Figure 3. JAK-STAT pathway in atopic dermatitis

When a cytokine binds to the intracellular domains of cytokine receptors, a conformational change is induced, and then JAK tyrosine kinases are activated, resulting in phosphorylation of tyrosine residues in the receptor's intracellular domain. The phosphorylation of receptor subunits allows for the recruitment of Signal Transducers and Activator of Transcription (STATs). Phosphorylated STATs are activated, dimerized and translocated to the nucleus to regulate target gene expression.

Figure 4. Forest plot for proportion of patients who achieved EASI 75 in adolescents

The figure shows odds ratio and 95% CI of patients achieved EASI 75 in studies evaluated the efficacy of biologics and JAKs in adolescents treated between 12 and 16 Weeks.

*These adult studies included from 10% to 22% adolescents.

EASI 75; 75% reduction in Eczema Area and Severity Index
Figure 5: Proportion of children aged 6 months to 12 years who achieved EASI 75 on Dupilumab treatment

The figure shows the 3 studies that evaluated efficacy of dupilumab in children aged from 6 months to 12 years. Y axis shows the proportion of participants achieved EASI 75. Label on each bar shows the treatment regimen.

EASI 75; 75% reduction in Eczema Area and Severity Index
Reference:
4. Abuabara K, Margolis DJ. Do children really outgrow their eczema, or is there more than one eczema? J Allergy Clin Immunol 2013;132:1139-40.


91. van Vollenhoven R, Takeuchi T, Pangan AL, Friedman A, Mohamed MEF, Chen S, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with...


Subtypes of adults with atopic dermatitis. Approximately 40%-60% of adults with atopic dermatitis are characterized by an early infancy-onset and chronic persisting course into adulthood. At birth, low levels of gamma interferon and increased level of type 2 cytokine producing cord blood T are subsequently associated with infancy-onset atopic dermatitis. Early onset atopic dermatitis and allergic sensitization at early age are at increased risk of early onset persistent phenotype. Among infants of early onset atopic dermatitis, some develop systemic allergic disease such as food allergy, allergic rhinitis, and asthma. The figure is based on the findings described by reference 8-13,15,16.
Table 1. Phenotypes of atopic dermatitis by the age of onset

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Infancy</th>
<th>early childhood</th>
<th>late childhood</th>
<th>adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age</td>
<td>&lt; 2 years</td>
<td>2≤age&lt;6</td>
<td>12≤age&lt;6</td>
<td>12≤age&lt;18</td>
</tr>
<tr>
<td>Inhalant allergen sensitization</td>
<td>More common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid disease</td>
<td>Asthma</td>
<td>FA</td>
<td>AR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Periauricular, Face</td>
<td></td>
<td>Extremities</td>
<td>Additional lesions of forehead and neck</td>
</tr>
<tr>
<td>Peripheral blood immune profiles</td>
<td>CLA^+ Th1 cells</td>
<td>Suppressed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Th2 cells</td>
<td>Similarly expanded across all ages</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-22</td>
<td>Increases with age from infancy to adolescence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Common features of Th2 and Th22 skewing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High Th17 cytokines</td>
<td></td>
<td>High Th1 cytokines</td>
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</table>

Table 2. Phenotypes of atopic dermatitis by atopic status

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Extrinsic</th>
<th>Intrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>high</td>
<td>Normal</td>
</tr>
<tr>
<td>Specific IgE</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Atopic background (personal/familial)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Sex predominance</td>
<td>female</td>
<td>none</td>
</tr>
<tr>
<td>Peripheral blood and skin</td>
<td>Th1, Th17/22 higher</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Th2</td>
<td>Similar</td>
</tr>
<tr>
<td>Antimicrobial peptide</td>
<td>lower</td>
<td>higher</td>
</tr>
</tbody>
</table>

Table 3. Phenotypes of atopic dermatitis by stage

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Erythematous papules and vesicles, oozing</td>
<td>Scaly patches and palques, lichenification,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nodules within plaques, hyperpigmentation/hypopigmentation</td>
</tr>
<tr>
<td>Histology</td>
<td>Spongiosis/edema between</td>
<td>Less pronounced epidermal spongiosis, marked thickening of the epidermis,</td>
</tr>
<tr>
<td>Skin</td>
<td>Antimicrobial peptide</td>
<td>Cytokines</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Atopic background (personal/familial)</td>
<td>+</td>
<td>Higher Th2, Th1, Th17</td>
</tr>
<tr>
<td>Sex predominance</td>
<td>female</td>
<td>-</td>
</tr>
<tr>
<td>Th1, Th17/22 (peripheral blood and skin)</td>
<td>Higher</td>
<td>Similar</td>
</tr>
</tbody>
</table>

Table 4. Summary of phase 3 studies for the use of systemic biologics and JAKi for AD treatment in pediatrics age:

<table>
<thead>
<tr>
<th>Medication (Mechanism)</th>
<th>Age, years (n)</th>
<th>Study design (Duration, week)</th>
<th>Regimen, mg</th>
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<tbody>
<tr>
<td><strong>Dupilumab</strong> (IL-4/IL-13 antagonist)</td>
<td>12-17 (251)</td>
<td>Blinded Monotherapy (16)</td>
<td>q2 wk: 200 mg &lt;60 kg, 300 mg ≥60 kg q 4 wk 300 mg</td>
<td>q2 wk, 41.5% q4 wk, 38.1%. placebo 8.2%</td>
<td>≥ 5% of patients: Conjunctivitis, injection site reaction.</td>
</tr>
<tr>
<td>6-11 (367)</td>
<td>Blinded Plus TCS (16)</td>
<td>q2 wk: 100 mg &lt; 30 kg 200 mg ≥ 30 kg q4 wk: 300 mg</td>
<td>q2 wk, 67.2% q4 wk, 69.7%. placebo 26.8%</td>
<td>≥ 5% of patients: Conjunctivitis, injection site reaction.</td>
<td></td>
</tr>
<tr>
<td>6-12 years (33)</td>
<td>Open label extension concomitant topical tx. (52)</td>
<td>qwk: 2 mg/kg 4 mg/kg</td>
<td>At 16 wk: 2 mg: 59% 4 mg: 73% At 52 wk: 2 mg: 94% 4 mg: 75%</td>
<td>Each participant had at least 3% of patients: Conjunctivitis and herpes viral infection.</td>
<td></td>
</tr>
<tr>
<td>6 months to 6 years (162)</td>
<td>Blinded Plus TCS (16)</td>
<td>q4wk 200 mg &lt; 15 kg 300 mg ≥ 15 kg</td>
<td>Tx: 53% Placebo 11%</td>
<td>Conjunctivitis and herpes viral infection.</td>
<td></td>
</tr>
<tr>
<td><strong>Lebrikizumab</strong> (IL-13 antagonist)</td>
<td>12 – 17 (52)</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td><strong>Tralokinumab</strong> (IL-13 antagonist)</td>
<td>12 to 17 (301)</td>
<td>Phase 3 Blinded Monotherapy (16)</td>
<td>q2wk: 150mg 300mg placebo</td>
<td>Initial tx: 150 mg: 28.6% 300 mg: 27.8% Placebo: 6.4%</td>
<td>≥ 5% of patients: Upper respiratory tract infection site reaction.</td>
</tr>
<tr>
<td><strong>Nemolizumab</strong> (IL-31 antagonist)</td>
<td>13-18 (143)</td>
<td>Blinded Concomitant topical tx. (16)</td>
<td>q4 wk: 60 mg</td>
<td>drug 25.9% Placebo 18.1%</td>
<td>≥ 3% of patients: Injection site reaction, abnormally increased blood creatine kinase</td>
</tr>
<tr>
<td><strong>Baricitinib</strong> (JAK 1/2 inhibitor)</td>
<td>2-17 years (16)</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td><strong>Upadacitinib</strong> (JAK 1 inhibitor)</td>
<td>12-75</td>
<td>MeasureUp1 (847) MeasureUp2 (836)</td>
<td>Blinded Monotherapy (16)</td>
<td>Measure up 1 15 mg 30 mg Placebo 15 mg 99.6% 30 mg 79.7% Placebo 16.3%</td>
<td>Measure up 2</td>
</tr>
<tr>
<td>Age Range</td>
<td>Treatment Details</td>
<td>Response Rates</td>
<td>Adverse Events</td>
<td></td>
<td></td>
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<tr>
<td>-----------</td>
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</tr>
<tr>
<td>12-75 AD Up (901)</td>
<td>Blinded Plus TCS (16)</td>
<td>15 mg: 60.1% 30 mg: 72.9% Placebo: 13.3%</td>
<td>≥ 5% of patients Acne, oral herpes, increased creatine phosphokinase.</td>
<td></td>
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</tr>
<tr>
<td>Abrocitinib (JAK 1 inhibitor)</td>
<td>12 to ≥ 65* (387)</td>
<td>Blinded Monotherapy (12)</td>
<td>100 mg: 40% 200 mg: 63% Placebo: 12%</td>
<td>≥ 3% of patients: GIT upset†, headache.</td>
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</tr>
<tr>
<td>12 to ≥ 65* (391)</td>
<td>Blinded Monotherapy (12)</td>
<td>100 mg: 44.5% 200 mg: 61.0% Placebo: 10.4%</td>
<td>≥ 3% of patients: GIT upset†, acne, headache, increased blood creatine phosphokinase, thrombocytopenia.</td>
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<tr>
<td>12-17 (285)</td>
<td>Blinded Concomitant topical tx. (12)</td>
<td>100 mg: 68.5% 200 mg: 72.0% Placebo: 41.5%</td>
<td>≥ 3% treatment of patients GIT upset†, acne, increased creatine phosphokinase.</td>
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</tbody>
</table>

EASI 75; 75% reduction in Eczema Area and Severity Index, Wk; week, tx; treatment, TEAE; Treatment Emergent Adverse Event, TCS; topical corticosteroid, AD; atopic dermatitis, AESI; Adverse Event of Special Interest, GIT; gastrointestinal tract.

* no upper limit for the age
†GIT upset included nausea, vomiting, and upper abdominal pain
Risk factors for persistence into adulthood

- Onset less than 2 years of age
- Greater severity

Figure 1 or Grapical abstract
Figure 2

**Impaired Epidermal Barrier**
- ↓ barrier structural protein, intercellular lipid, enzymes
- ↓ AMPs
- ↑ skin pH
- ↑ Ag penetration
- ↑ TEWL

**Immune Dysregulation**
- ↑ alamins
- ↑ Th2, ILC2
- ↑ IgE

**Itch**
- Pruritogens: IL-31, TSLP, IL-4, ...

**Microbiome dysbiosis**
- ↓ skin microbiome diversity
- ↑ *S. aureus*
<table>
<thead>
<tr>
<th>Cytokines</th>
<th>IL-31</th>
<th>IL-4</th>
<th>IL-13</th>
<th>IL-5</th>
<th>TSLP</th>
<th>IL-22</th>
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</thead>
<tbody>
<tr>
<td><strong>JAKs</strong></td>
<td></td>
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<tr>
<td>JAK1/JAK2</td>
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<td>JAK1/JAK3</td>
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<td>JAK1/TYK2</td>
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</tbody>
</table>

**Oral JAK inhibitors accepted for children**
- Abrocitinib: Selective JAK1
- Upadacitinib: Selective JAK1
- Baricitinib: Selective JAK1 and JAK2

**Figure 3**

Diagram showing Cytokine receptor binding, JAKs, STAT activation, and nuclear transcription.
Adolescent studies included adolescent

*Adult studies included adolescent

- Upadacitinib 30 mg/d
- Upadacitinib 15 mg/d
- Upadacitinib 30 mg/d
- Upadacitinib 15 mg/d
- Abrocitinib 200 mg/d
- Abrocitinib 100 mg/d
- Abrocitinib 200 mg/d
- Abrocitinib 100 mg/d
- Abrocitinib 200 mg/d
- Abrocitinib 100 mg/d
- Nemolizumab 60 mg/4wk
- Tralokinumab 300 mg/2wk
- Tralokinumab 150 mg/2wk
- Dupilumab 300 mg/4wk
- Dupilumab 200-300 mg/2wk

Odds ratio

Mean deference (95% CI)
Figure 5

**Age of participants and study duration**

<table>
<thead>
<tr>
<th>Age</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months – 6 years</td>
<td>16 weeks</td>
</tr>
<tr>
<td>6 – 11 years</td>
<td>16 weeks</td>
</tr>
<tr>
<td>6 - 12 years</td>
<td>52 weeks</td>
</tr>
</tbody>
</table>

**Dosage**

- Dupilumab + Topical treatment
  - 200-300mg/4wk
  - 100-200mg/4wk
  - 2mg/kg/wk

- Placebo + Topical treatment
  - 100-200mg/2wk
  - 4mg/kg/wk