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# Recent Advances in Atopic Dermatitis

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## Abstract

The prevalence and disease burden of atopic dermatitis (AD) is substantial. AD causes significant impairment in quality of life. It is also associated with mental disorders as well as cardiovascular diseases. Many factors including race, environment, skin barrier dysfunction, immune regulatory abnormalities, and microbiome have been reported to affect the pathophysiology of AD. A variety of cell types including Th2, Th17, Th22, and type 2 innate lymphoid cells contribute to AD. Cytokines from these immune cells cause abnormal epidermal differentiation and skin barrier dysfunction. Moreover, microbial dysbiosis and deficiency of antimicrobial peptides result in *Staphylococcus aureus* infection. Recently, new drugs have been successfully launched to target polarized immune pathways that lead to moderate-to-severe AD.

### Keywords

Atopic dermatitis; Epidermal barrier; Microbiome; Biologics

## Introduction

Atopic dermatitis (AD) is characterized by immune dysregulation, epidermal barrier defects, and microbial dysbiosis [1**, 2*, 3, 4**]. The prevalence of AD has increased in both children and adults [5*,6]. AD is associated with mental problems, cardiovascular diseases, autoimmunity, and recurrent infections [6–8]. Additionally, AD causes marked impairment to quality of life for patients and their families [6,7]. Recently, researchers have advanced our understanding of the pathophysiology of AD. Many factors including race, onset of AD, environmental factors, altered epidermal lipid profiles, immune dysregulation, and microbial

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dysbiosis play critical roles in AD and modify the course of this common skin disease [3,9,10]. New strategies, including the correction of microbial dysbiosis and new biologics and small molecules, are being used to control disease activity in patients with moderate-to-severe AD.

## Epidemiology

Pediatric AD is significantly associated with mental disorders including impairment of emotional behavior, peer relationships, and attention [11]. AD is also associated with depression and suicidal ideations in children and adults [6,7]. A systematic review and meta-analysis of cohort studies has demonstrated that AD is associated with increased risk of cardiovascular complications such as myocardial infarction, stroke, ischemic stroke, angina, and heart failure along with anaphylaxis to egg and milk [8,12]. More attention should therefore be paid to the comorbidities of AD.

Recently, there has been great interest on AD subgroups. Using data from 1,437 mother-child pairs of a prospective prebirth cohort in eastern Massachusetts, it was found that early childhood AD was more likely to persist in non-Hispanic blacks (aOR, 6.26; 95% CI, 2.32–16.88) and Hispanics (aOR, 6.42; 95% CI, 1.93–21.41) compared to non-Hispanic whites [9]. In another prospective cohort study of 4,898 women and their children in 20 large cities, female gender (aOR, 1.56; 95% CI, 1.02–2.37) and black race (aOR, 1.80; 95% CI, 1.07–3.01) were associated with persistent AD through ages 5, 9, and 15 years [13]. These findings indicate that AD persistence is higher in specific subgroups and would be important to consider in our understanding of AD phenotypes and endotypes.

Clinically, it is known that AD develops primarily in children and can resolve over time. However, there have been controversies about persistence of AD beyond childhood. In a systematic review and meta-analysis of population-based longitudinal studies of AD patients ranging from age 3 months to 26 years, the percentage decrease in prevalence after age 12 was only 1% [14*]. These investigators suggested that this is due to a combination of factors including disease persistence, decreased remission, and later-onset disease. In fact, the estimated prevalence of AD among US adults with a mean age of 51.25 years is 7.3%, indicating that a substantial number of people in this age group have AD [6]. In particular, 26.1% of AD in adults is an adult-onset disease which has a distinct clinical phenotype according to Lee *et al* [5*]. Increasing awareness of adult AD is needed for timely diagnosis and proper management.

## Environmental factors

Our understanding of environmental factors that trigger AD is critical because they are modifiable. A recent cross-sectional study among South African toddlers aged 12–36 months reported that consumption of fermented milk products is strongly associated with reduced AD in an urban cohort. However, this effect was not found in the rural population, suggesting a role for urbanization and loss of gut microbial diversity in AD development [10]. A systematic review and meta-analysis revealed that there was a significant association between AD and fall birth (OR, 1.16; 95% CI, 1.06–1.28; $P$=0.0018) and winter birth (OR,

1.15; 95% CI, 1.04–1.27; $P$=0.0076) in the northern hemisphere when compared to spring birth. Although the exact mechanism remains unclear, the authors proposed reduced ultraviolet radiation (UVR) exposure, increased immune activity, and increased air pollution in specific seasons contribute to a higher prevalence of AD [15].

Air pollution is a growing concern with urbanization and industrialization. Rutter *et al* collected the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3 survey data of 546,348 children from 53 countries and assessed the individual- and school-level effects of environmental factors to exclude reverse causation. They found that current exposure to heavy traffic is significantly associated with eczema symptoms in 13–14-year-olds during the previous 12 months [16]. In a consortium of six birth cohorts from Europe and Canada, genetic risk scores from glutathione S-transferase P1, tumor necrosis factor, Toll-like receptor (TLR)-2, and TLR-4 single-nucleotide polymorphisms were associated with AD up to the age of 2 years [17]. Furthermore, oxidative stress and inflammation were associated with the prevalence of childhood AD and they may modify susceptibility to air pollution-induced AD [17]. However, traffic-related air pollution (TRAP) did not show an association with AD in the general population [17]. In elderly participants over age 50, exposure to TRAP was significantly associated with increased odds of incident eczema and this effect was more pronounced with nonatopic eczema [18]. Therefore, exposure to air pollution may involve the development or aggravation of AD through oxidative stress and inflammation, especially in susceptible children and elderly. However, further study is needed to clarify the association between TRAP and AD.

The concept of exposome has been introduced to improve our understanding of the pathophysiology of AD. Exposome is the sum of environmental influences throughout an individual's lifetime. Exposomal domains are stratified into external nonspecific (e.g. climate, migration, urbanization), external specific (e.g. humidity, UVR, diet, pollution, allergens, water hardness), and internal (e.g. microbiome) exposures [19*]. Future research will focus on exposome characterization and whether its modification alters the disease course of AD [19*].

## Epidermal barrier

Epidermal barrier dysfunction contributes to the development of AD and food allergy [2*]. Type 2 cytokines inhibit the expression of structural cornified barrier proteins such as filaggrin (FLG), loricrin, involucrin, antimicrobial peptides (AMPs), and tight junctions [2*,3]. IL-17-producing T helper (Th) 17 and Th22 subsets can also be highly upregulated in certain AD subtypes and are associated with abnormal keratinocyte differentiation and epidermal barrier dysfunction [3]. FLG is a key epidermal barrier protein required for formation of the stratum corneum (SC) and is influenced by environmental factors such as climate, pollution, and microbiome [20,21]. A recent study demonstrated that the epidermal mammalian target of rapamycin complex 2 activity orchestrated epidermal barrier formation through FLG processing and *de novo* epidermal lipogenesis [22*]. Additionally, siRNA-knockdown of EMSY, also characterized as a transcriptional regulator, increased the number of layers within the SC and the expression of corneodesmosomes and FLG [23]. These studies have focused on novel mechanistic insights into epidermal barrier formation, which

may be used as a future therapeutic target to improve epidermal barrier conditions [22*,23]. Recently, human keratinocyte proline-rich proteins in the upper part of the granular layer have also been reported to play a crucial role in skin barrier function and percutaneous immune responses [24].

The corneocyte lipid envelope becomes a hydrophobic impermeable epidermal layer that prevents water loss and antigen penetration [3]. AD skin is associated with a reduced free fatty acid chain length and an increased proportion of ceramides with an unsaturated acyl-chain and sphingosine subclass. This correlates with an aberrant lipid organization and decreased skin barrier function [25]. It is also known that the ratio between ω-esterified fatty acid sphingosine (EOS) ceramides and nonhydroxy fatty acid sphingosine (NS) ceramides is higher in AD patients than those in normal controls [1**]. Interestingly, a recent study demonstrated that Th2 cytokines downregulated fatty acid elongases 3 and 6 in human keratinocytes in a signal transducer and activator of transcription (STAT)-6-dependent way, indicating the role of Th2 immune activation in epidermal lipid metabolism in AD patients [26**]. *Staphylococcus aureus (S. aureus)*-colonized AD patients reveal lower levels of long chain ceramides than those without *S. aureus* colonization. This suggests that *S. aureus* colonization affects lipid composition and enhances skin barrier impairment [27].

## Immune dysregulation

It is well known that Th2, Th17, Th22, and type 2 innate lymphoid cells (ILC2) play central roles in AD pathobiology [2*,3,20] (Figure 1). Researchers have recently found additional cytokines that are significant to the pathogenesis of AD. Kamijo *et al* have reported that IL-26, which is produced by Th17 cells, induces production of Th2 and Th17-associated cytokines such as IL-4, IL-13, IL-17A, IL-33, etc. in a mouse model of AD [28**]. Therefore, it has been suggested that IL-26 may exacerbate AD and act as an important bridge between Th2 and Th17 responses in AD skin. It has been known that regulatory B cells suppress inflammation by the secretion of IL-10. Moreover, it has recently been reported that IL-10-producing regulatory B cells are decreased in severe AD patients compared to mild AD patients and normal control subjects [29].

*S. aureus* infection correlates with type 2 responses in AD skin, but it has not been elucidated how *S. aureus* infection aggravates type 2 inflammation in AD skin. Brauweiler *et al* have demonstrated that *S. aureus* lipoteichoic acid inhibits expression of skin barrier proteins [30] and causes the expression of IL-4 from basophil by the production of thymic stromal lymphopoietin (TSLP) [31]. Ryffel *et al* have reported that basophil and ILC2 contribute to IL-33 mediated AD-like skin inflammation without adaptive immune cells [32]. TSLP upregulates Fc receptor γ receptors on antigen-presenting cells through STAT-5 and induces Th2/Th17 polarization through dectin-2 [33].

## Cutaneous microbiome

The commensal microbiome communicates with host immune systems and plays a key role in maintaining cutaneous homeostasis [34,35*]. Commensal bacteria are able to produce AMPs and prevent invasion of pathogenic microorganisms such as *S. aureus* on the skin of

healthy subjects [34,35]. Decreased microbial diversity and deficiency of AMPs, which lead to frequent *S. aureus* infection and microbial dysbiosis, are characteristic findings in AD skin [4**,35*]. *S. aureus* infection aggravates AD skin and is strongly associated with the severity of AD [4**,34].

Conversely, normalization of microbial signature by transplantation of cutaneous commensal bacteria reduces *S. aureus* colonization, skin inflammation, and promotes clinical improvement of AD [34,35*]. Callewaert *et al* have recently reported that an antibody to IL-4 receptor α (dupilumab) decreases *S. aureus* abundance and increases microbial diversity in AD skin [36]. It has been reported that aryl hydrocarbon receptor (AHR) plays a major role in cutaneous microbial-host interactions [37,38]. Yu *et al* have demonstrated that skin microbiome-derived tryptophan metabolites, which are decreased in AD skin, may attenuate skin inflammation through the AHR [37]. Additionally, topical treatment of coal tar upregulates the levels of AMPs in an AHR dependent manner and changes microbiota composition toward that of healthy subjects by decreasing *Staphylococcal* abundance and increasing *Propionibacterium* abundance [38].

## Clinical application of new drug targets

As AD treatment has begun to move toward precision medicine, various biologic and small molecule agents have been developed to block specific cytokines, cytokine receptors, or transcription factors (Table 1). Dupilumab is a monoclonal antibody that reduces type 2 inflammtion by antagonizing IL-4 and IL-13 action and has been approved by the US Food and Drug Administration for patients with moderate-to-severe AD [39,40]. In a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, subcutaneous injections of dupilumab monotherapy in adolescents every 2 weeks or 4 weeks led to a significantly higher proportion of patients with EASI75 improvement at week 16 [39]. In this study, safety was acceptable [39]. Clinical trials of many new biologics are in progress to assess their efficacy and safety in both adults and pediatric populations [40–45, 46**, 47–53].

Indications are expanding from adults to children and formulations are becoming more diverse, ranging from injections to topical cream and oral forms [42,44,48]. These drugs are targeting various key molecules responsible for skin inflammation, i.e., IL-4 receptor α chain, IL-31 receptor α subunit, TSLP, IL-13, IL-22, OX40, AHR, phosphodiesterase 4 (PDE4), and Janus kinase (JAK). Most of the newly developed biologics and small molecule antagonists have been reported to be efficacious and well tolerated [47–49,52]. Further research in large populations of AD are needed to improve therapeutic outcomes of precision medicine and to guarantee drug safety.

## Conclusions

AD is a heterogenous skin disease charcterized by skin barrier dysfunction, systemic immune dysregulation, systemic comorbidities, and microbial dysbiosis. In recent years, a better understanding of AD has been achieved by various research investigations. New

treatments such as microbial skin transplantation, biologics, and small molecular antagonists targeting key immune pathways will improve our treatment strategies in AD.

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Conflict of interest

Donald YM Leung has consulted for Regeneron, Boehringer-Ingelheim, and Sanofi/Genzyme. He has also received grant support from MedImmune/Astra-Zeneca, Incyt,e and Pfizer. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Abbreviations

| | |
|---|---|
| **AD** | atopic dermatitis |
| **AE** | adverse event |
| **AHR** | aryl hydrocarbon receptor |
| **AMP** | antimicrobial peptide |
| **BSA** | body surface area |
| **CI** | confidence interval |
| **EASI** | eczema area and severity index |
| **EOS ceramide** | ω-esterified fatty acid sphingosine ceramide |
| **FLG** | filaggrin |
| **IGA** | investigator’s global assessment |
| **ILC2** | type 2 innate lymphoid cell |
| **JAK** | Janus kinase |
| **NS ceramide** | nonhydroxy fatty acid sphingosine ceramide |
| **OR** | odds ratio |
| **PDE4** | phosphodiesterase 4 |
| ***S. aureus*** | *Staphylococcus aureus* |
| **SC** | stratum corneum |
| **SCORAD** | scoring of atopic dermatitis |
| **STAT** | signal transducer and activator of transcription |

| | |
|---|---|
| **TEAE** | treatment-emergent adverse event |
| **Th** | T helper |
| **TJ** | tight junction |
| **TLR** | Toll-like receptor |
| **TRAP** | traffic-related air pollution |
| **TSLP** | thymic stromal lymphopoietin |
| **UVR** | ultraviolet radiation |

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* of special interest

** of outstanding interest


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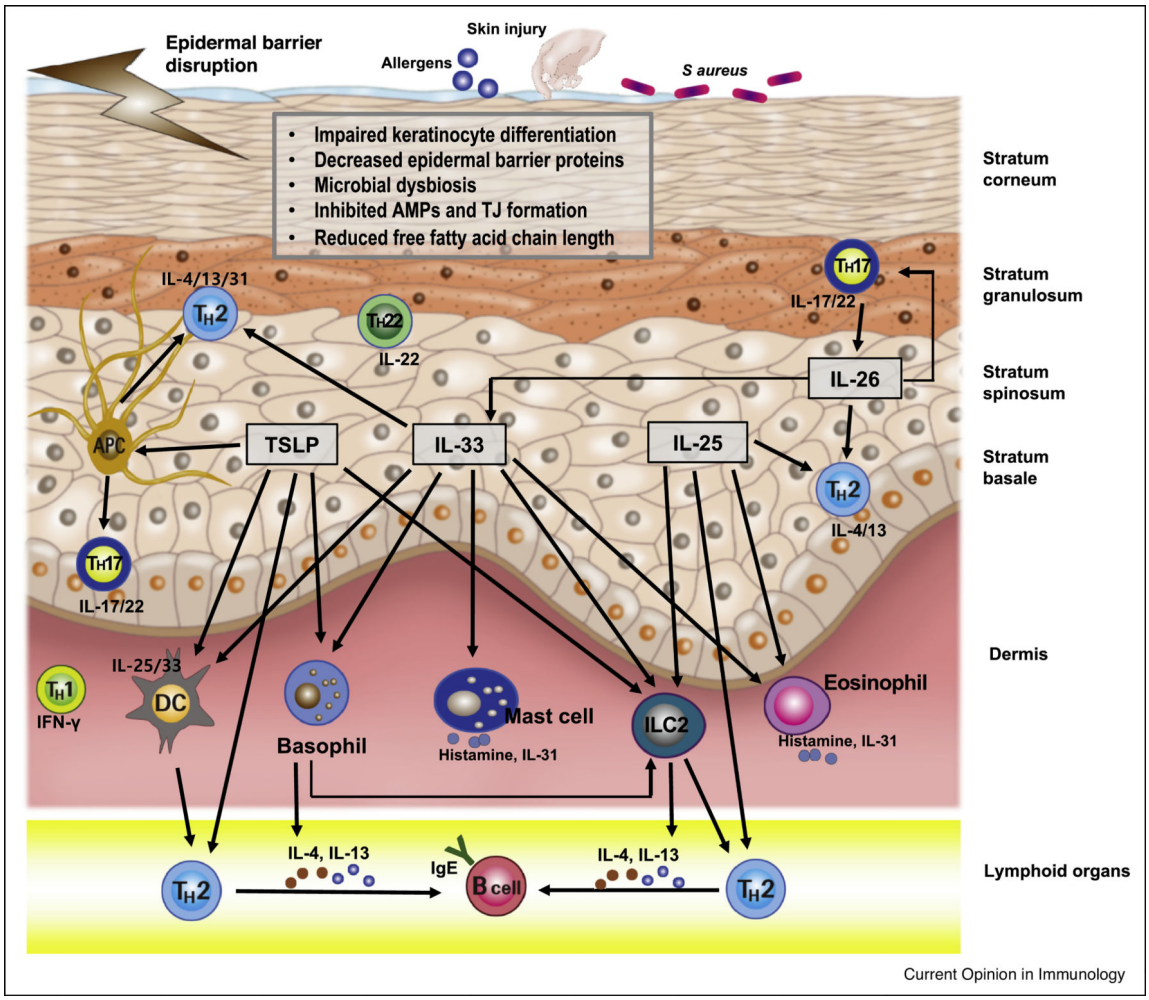


**Figure 1. Pathophysiology of atopic dermatitis.**

Epidermal barrier defects, cutaneous dysbiosis, and immune dysregulation play important roles in the pathophysiology of AD. TSLP, IL-25, IL-33, and ILC2 induce production of Th2, Th17, and Th22 cytokines directly or indirectly. TSLP activates antigen presenting cells, dendritic cells, basophil, and ILC2 to produce Th2 and Th17 cytokines. IL-26 from Th17 cells induces production of IL-4, IL-13, IL-17A, and IL-33.

*Abbreviations:* AMPs, antimicrobial peptides; ILC2, type 2 innate lymphoid cell; Th2, T helper type 2; Th17, T helper type 17; Th22, T helper type 22; TJ, tight junction; TSLP, thymic stromal lymphopoietin.

**Table 1.**

Summary of recently published clinical trials and retrospective review of new drugs in atopic dermatitis

| Biologic agents | Target | Phase | Region | Study population | Administration | Study duration | Efficacy | Safety | Reference |
|---|---|---|---|---|---|---|---|---|---|
| **In adults and adolescents** | | | | | | | | | |
| Dupilumab | IL4 receptor alpha chain | Real-life multicenter retrospective cohort study | France | 241 adults (>18 years) with moderate-to-severe AD | Subcutaneous injection | 3.8±3.7 months | Significant improvement in disease severity at 3 months of treatment | High frequency of conjunctivitis and eosinophilia | 40 |
| Dupilumab | IL4 receptor alpha chain | Phase 3, RCT (3-arm trial) | USA, Canada | 251 adolescents (12–17 years) with moderate-to-severe AD | Subcutaneous injections with dulipumab 200 mg (baseline weight <60 kg) or 300 mg (baseline weight ≥ 60 kg) every 2 weeks, 300 mg every 4 weeks, or placebo | 16 weeks | Significant improvement in AD signs, symptoms and quality of life; efficacy of the every-2-week regimen was generally superior to the every-4-week regimen | No significant difference between dupilumab and placebo groups; safety is acceptable | 39 |
| Nemolizumab | IL31 receptor alpha subunit | Phase 2b, RCT (4-arm trial) | North America (USA, Canada), Europe (France, Germany, Poland), Australia | 226 adults with moderate-to-severe AD | Subcutaneous injections with a loading dose of 20, 60, or 90 mg on day 1, followed by 10, 30, or 90 mg, respectively, every 4 weeks | 20-week treatment and 12 week follow-up | Rapid and sustained improvement with maximal efficacy observed at 30 mg | No significant difference between treatment and placebo groups; safe and well tolerated | 43 |
| Tezepelumab | TSLP | Phase 2a, RCT (2-arm trial) | Australia, Canada, Germany, Hungary, New Zealand, USA | 113 adults (18–75 years) with moderate-to-severe AD | Subcutaneous injections of 280 mg every 2 weeks plus class 3 topical corticosteroids | 12 weeks | No significant difference between treatment and placebo groups | No significant difference between treatment and placebo groups | 48 |
| Tralokinumab | IL13 | Phase 2b, RCT (4-arm trial) | Australia, Canada, Germany, Japan, Poland, USA | 299 adults (18–75 years) with moderate-to-severe AD | Subcutaneous injections with 45, 150, or 300 mg of tralokinumab or placebo every 4 weeks | 12 weeks | Early and sustained improvements in AD symptoms | No significant difference between treatment and placebo groups; safe and well tolerated | 51 |
| GBR 830 | OX40 | Phase 2a, RCT (2-arm trial) | USA, Canada | 64 adults with moderate-to-severe AD | Two intravenous administration of 10 mg/kg 4 weeks apart (day 1, day 29) | 4-week treatment and 14 week follow-up | Significant progressive tissue and clinical improvements until day 71 (42 days after the last dose) | Well tolerated with equal TEAE distribution | 45 |

| Biologic agents | Target | Phase | Region | Study population | Administration | Study duration | Efficacy | Safety | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Fezakinumab | IL22 | Phase 2a, RCT (2-arm trial) | USA | 59 adults with moderate-to-severe AD | Intravenous administration with a loading dose of 600 mg followed by 300 mg every 2 weeks for 10 weeks | 10-week treatment and 10 week follow-up | A significant decline in disease severity for severe AD patients; a profound effect of IL22 blockade on multiple inflammatory pathways | No significant difference between treatment and placebo groups | 50,53 |
| Ruxolitinib | JAK1/ JAK2 | Phase 2, RCT (6-arm trial) | USA, Canada | 252 adults (18–70 years) with history of AD > 2 years, IGA score of 2 or 3 and BSA involvement of 3%–20% | 0.15% RUX cream qd, 0.5% RUX cream qd, 1.5% RUX cream qd, 1.5% RUX cream bid, vehicle cream bid, 0.1% triamcinolone cream bid | 8-week of double-blind treatment, 4-week of open-label treatment and 4-week of follow-up | Rapid and sustained improvement in AD symptoms | Unremarkable safety profile with no notable systemic effects and good tolerability | 41 |
| Tapina rof | AHR | Phase 2, RCT (6-arm trial) | USA, Japan | 247 adolescents and adults (12–65 years) with moderate-to-severe AD | 1% tapinarof cream bid, 1% tapinarof cream qd, 0.5% tapinarof cream bid, 0.5% tapinarof cream qd, vehicle bid, vehicle qd | 12-week treatment and 4-week follow-up | Significantly higher success rate in the treatment grouop | More TEAEs with mild to moderate intensity in treatment group | 47 |
| Apremilast | PDE4 | Phase 2, RCT (3-arm trial) | North America, Japan | 185 adults (≥18 years) with moderate-to-severe AD | 30 mg tables bid (APR30), apremilast 40 mg tables bid (APR40), placebo | 12 weeks | Modest clinical efficacy for APR40 with decreased AD-related biomarkers | More frequent AEs including cellulitis in APR40-treated group, leading to discontinuation of treatment | 49 |
| Baricitinib | JAK1/ JAK2 | Phase 2, RCT (3-arm trial) | USA, Japan | 124 adults (26–52 years) with moderate-to-severe AD | 2 mg tablet qd, 4 mg baricitinib tablet qd, placebo qd | 16 weeks | Significantly reduced inflammation and pruritus | More frequent headache, increased creatine phosphokinse level and nasopharyngitis in 4 mg baricitinib-treated group | 52 |
| **In children** | | | | | | | | | |
| Dupilumab | IL4 receptor alpha chain | Multi-center retrospective review of off-label use | USA | 111 children with the age of 13.0±3.9 years (range 3.1 to 18.0) with moderate-to-severe AD | Subcutaneous injections of a mean of 8.7 mg/kg (range, 4–15.5; SD 2.2) loading dose followed by a mean of 5.1 mg/kg (range, 2.0–15.3; SD 2.2) maintenance dose every other week | 9 weeks | 64.3% experienced ≥ 2-point IGA improvement; 22.1% reported a 1-point improvement, and 12.6% experienced no improvement. | AEs are comparable to previous adolescent and adult trials. | 42 |

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| Biologic agents | Target | Phase | Region | Study population | Administration | Study duration | Efficacy | Safety | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Delgocitinib | JAK (JAK1/ JAK2/ JAK3/ tyrosine kinase) | Phase 2, RCT (3-arm trial) | Japan | 103 children (2–15 years) with AD (modified EASI ≥ 5, IGA ≥ 2 and BSA involvement of 5%–30%) | 0.25% or 0.5% delgocitinib ointment bid, placebo bid | 4 weeks | Significant improvement in clinical signs and symptoms | No significant difference between treatment and placebo groups; mild AEs with no serious events | 44 |