REVIEW

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Biologics and oral small-molecule inhibitors for treatment of pediatric atopic dermatitis: Opportunities and challenges

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ABSTRACT

Atopic dermatitis (AD) is a complex disease characterized by recurrent eczematous lesions and refractory pruritus that drastically impairs quality of life. Due to the chronic and relapsing course, patients are easily trapped in the debilitating condition. Classical therapies show limitations, especially for patients with moderate-to-severe phenotypes. Advanced new insights in targeted therapies exhibit great application prospects which were reinforced by the more profound understanding of the disease pathogenesis. However, the sustained efficiency, biosafety, and long-term benefits still remain in further exploration. This review summarizes recent clinical studies on oral small-molecule inhibitors and biological agents for pediatric AD patients, which provides the latest frontiers to clinicians.

KEYWORDS

Atopic dermatitis, Biologics, Clinical trials, Dupilumab, Pediatrics, Small-molecule inhibitors

INTRODUCTION

Atopic dermatitis (AD) is one of the most prevalent systemic inflammatory diseases characterized by chronic, recurrent eczema and refractory pruritis, often developing in childhood and persisting into adulthood.[1] The incidence and prevalence of AD have increased over the past several decades.[1,2] Notably susceptible are infants, with prevalence rates ranging from 15% to 20% in developed nations.[3] The chronic relapsing-remitting pattern of AD impairs the life quality of both patients and their family members and imposes psychological and financial burdens on them.[4]

The etiology of AD is intricate and multifaceted, involving interactions among immune dysregulation, genetic susceptibility, skin barrier dysfunction, and microbial imbalance.[1,2] Transcriptomic analysis of the skin of AD patients has revealed a predominant increase in type 2 cytokines in both acute and chronic skin lesions, including interleukin (IL)-13, IL-4, IL-5, and IL-31, indicating the strong activation of type 2 T helper (Th2) immune responses.[5] Type 2 cytokines, particularly IL-4 and IL-13, orchestrate the generation of immunoglobulin E (IgE) by B cells, along with the stimulation of immune cells like eosinophils and mast cells. These processes collectively contribute to the inflammatory milieu and the manifestation of pruritus symptoms.[5,6] Emerging as a pivotal participant, the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway has

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been implicated in AD to modulate multiple immune pathways driving cutaneous inflammation.[7] Recent findings underscore the significance of neuronal JAK1 signaling in chronic itch. Intriguingly, targeted JAK inhibition in individuals afflicted with persistent pruritus has shown potential in alleviating itch-related distress.[8] With a deeper understanding of AD's pathophysiology, biologics that target type 2 cytokines or receptors (e.g., dupilumab, nemolizumab, lebrikizumab, and tralokinumab), as well as small-molecular inhibitors (e.g., baricitinib, abrocitinib, and upadacitinib), have emerged as promising avenues. These hold the potential for enhanced efficacy and safety when compared to conventional oral immunosuppressive systemic regimens, particularly among adults grappling with uncontrolled moderate-to-severe AD.

The usage of biologics in treating pediatric patients with AD remains contentious due to concerns regarding their long-term safety. To date, dupilumab is the first and only biological agent approved by the US Food and Drug Administration (FDA) for children with moderate-to-severe AD. In a significant development, the FDA granted approval in 2022 for upadacitinib, an oral JAK inhibitor, for use in patients aged 12 years and older. Other emerging biologics and small-molecular drugs (nemolizumab, lebrikizumab, tralokinumab, abrocitinib, upadacitinib, omalizumab, etc.), currently in phase 2 and 3 clinical trials, also have shown potential efficacy in treating pediatric patients with AD.

In this review, we will focus on the emerging systemic biologics and systematic small-molecular inhibitors that intervene in the inflammatory pathways of AD, and discuss their mechanisms, safety, and efficacy in the treatment of pediatric AD with an update of the most recent clinical studies. The current completed clinical trials have been summarized in Table 1.

BIOLOGICS TARGETING TYPE 2 CYTOKINE RECEPTORS

Dupilumab

Dupilumab is a human monoclonal antibody targeting the shared α subunit of IL-4 and IL-13 receptors (IL-4R and IL-13R). This mechanism impedes the signaling of IL-4 and IL-13, pivotal Th2 cytokines that orchestrate inflammation in AD pathogenesis. FDA and European Medicines Agency approvals were secured by dupilumab in 2017 and 2019 respectively, for treating moderate-to-severe AD in adults and adolescents (≥12 years). It was successively approved by the FDA as the first biologics for children aged 6–12 years (in 2020) and those aged 6 months to 5 years (in 2022) with moderate-to-severe AD. Notably, dupilumab has demonstrated both efficacy and safety profiles in diverse type 2 immune disorders, including eosinophilic esophagitis, and was approved in use for chronic rhinosinusitis with nasal polyposis and moderate-to-severe asthma with eosinophilic phenotype.[9–11]

The efficacy and safety of dupilumab in pediatric AD

The efficacy and safety of dupilumab for children aged 6 months to younger than 6 years with moderate-to-severe AD was supported by LIBERTY AD PRE-SCHOOL (NCT03346434), a randomized, double-blinded, phase 3 trial.[12] Patients were randomly assigned to subcutaneous placebo or dupilumab (200 mg for body weight ≥5 kg–<15 kg or 300 mg for body weight ≥15 kg–<30 kg) every 4 weeks (Q4W) plus low-potency topical corticosteroids for 16 weeks. The results showed that significantly more patients in the dupilumab group than in the placebo group had Investigator's Global Assessment (IGA) 0–1 (28% *vs*. 4%, $P < 0.0001$) and Eczema Area and Severity Index (EASI)-75 (53% *vs*. 11%, $P < 0.0001$). The overall prevalence of adverse events (AEs) was similar between the two groups (64% *vs*. 74%, in dupilumab and placebo group, respectively), mostly infections and infestations (nasopharyngitis, upper respiratory tract infection, and molluscum contagiosum), and AD exacerbations. Skin infection incidence and AD exacerbations with dupilumab were lower than with placebo (12% *vs*. 24% and 13% *vs*. 32%, respectively). A higher incidence of narrow conjunctivitis occurred in the dupilumab group than in the placebo group (5% *vs*. 0%). This study showed that dupilumab can significantly improve symptoms of AD in children younger than 6 years, with acceptable safety and tolerance.[12]

The approval of dupilumab for adolescents aged 6–17 years with moderate-to-severe AD was supported by 3 phase III clinical trials, LIBERTY AD ADOL, LIBERTY AD PEDS, and their open-label extension study LIBERTY AD PED-open-label extension (OLE).

LIBERTY AD ADOL is a phase III clinical trial (NCT03054428) completed in June 2018.[13] A total of 251 adolescents aged 12 to 17 years with inadequately controlled moderate-to-severe AD received 16-week subcutaneous dupilumab injection regimes: 200 mg or 300 mg every 2 weeks (Q2W); or 300 mg Q4W; or placebo. The treatment of dupilumab showed a higher proportion of patients with EASI-75 improvement (41.5%, Q2W; 38.1%, Q4W; 8.2%, placebo) and a higher proportion of patients reaching IGA 0 or 1 (24.4%, Q2W; 17.9%, Q4W; 2.4%, placebo), both regimens, $P < 0.001$. Numerically, the Q2W regimen showed an efficacy superior to that of the Q4W regimen.[14] Post-hoc analyses of LIBERTY AD ADOL demonstrated that dupilumab provided clinically meaningful improvements in AD signs, symptoms, and quality of life (QoL).[15]

TABLE 1 Current clinical trials of biologics in pediatric atopic dermatitis (AD)

Clinical trials	Status	Study design	Patients (number, age)	Interventions	Primary outcomes measures	Results of primary outcomes	Adverse events
Dupilumab							
NCT02407756	Completed; completion date: March 31, 2016	Phase IIa, multicenter, OL study	$n = 40$; aged 6 to 17 years	Part A: once 2 mg/kg or 4 mg/kg SC dupilumab; Part B: 2 mg/kg or 4 mg/kg SC dupilumab weekly for 4 weeks	PK parameters, EASI scores	Nonlinear, target-mediated PK of dupilumab. A reduction of −34% ± 20% (2 mg/kg) and −51% ± 29% (4 mg/kg) of EASI scores	TEAEs: 50% (2 mg/kg) and 65% (4 mg/kg) in part A; 40% and 55% in part B. Frequently nasopharyngitis and AD exacerbation. SAEs: 5%, palpitations, infected AD and staphylococcal skin infection mostly reported
NCT03054428	Completed; completion date: June 5, 2018	Phase III, OLE, randomized, DB, multicenter, parallel-group study	$n = 251$; aged 12 to 17 years	Randomized (1:1:1) to 16-week treatment with SC injection of dupilumab, 200 mg or 300 mg Q2W; 300 mg Q4W, or matching placebo	Patients achieving EASI-75	Patients with EASI-75 improvement: 41.5%, Q2W; 38.1%, Q4W, with differences *vs.* placebo of 33.2% for Q2W and 29.9% for Q4W ($P < 0.001$). Efficacy of the Q2W regimen was generally superior to the Q4W regimen	TEAEs: 63.9% in Q4W group, 72.0% in Q2W group, and 69.4% in placebo; common TEAEs: infections and infestations, AD, skin infections, conjunctivitis, nasopharyngitis. Higher prevalence of conjunctivitis (Q2W, 9.8%; Q4W, 10.8%; placebo, 4.7%) and injection-site reactions (Q2W, 8.5%; Q4W, 6.0%; placebo, 3.5%), and lower nonherpetic skin infections (Q2W, 9.8%; Q4W, 9.6%; placebo, 18.8%)
NCT03345914	Completed; completion date: September 10, 2019	Phase III, randomized, DB study	$n = 367$; aged 6 to 11 years	Randomized (1:1:1) to 16-week treatment with SC injection of dupilumab, 300 mg dupilumab Q4W; or weight-based regimen of 100 mg or 200 mg Q2W, or matching placebo, all with concomitant TCS	Patients achieving IGA score of 0 or 1	At week 16, dupilumab + TCS regimens showed significantly better efficacy than placebo + TCS. Patients achieving IGA score of 0 or 1: Q2W + TCS, 29.5%; Q4W + TCS 32.8%; placebo + TCS, 11.4%. EASI-75 (67.2% and 69.7% *vs.* 26.8%; $P < 0.0001$)	Overall lower TEAEs incidence in the dupilumab than placebo groups (65.0%, 67.2% *vs.* 73.3%); 2 patients (1.7%) with serious TEAEs. Frequently infections and infestations, nasopharyngitis, upper respiratory tract infection, injection-site reactions, conjunctivitis
NCT03346434	Completed; completion date: July 28, 2022	Phase III, DB, placebo-controlled, parallel-group study	$n = 197$; aged 6 months to 6 years	Assigned (1:1) to 16-week treatment with SC injection of dupilumab (bodyweight ≥ 5 kg to < 15 kg: 200 mg; bodyweight ≥ 15 kg to < 30 kg: 300 mg) Q4W, or matching placebo, plus low-potency TCS	Patients achieving IGA score of 0 or 1	At week 16, dupilumab + TCS regimens showed significantly better efficacy than placebo + TCS. Patients achieving IGA score of 0 or 1: 28% *vs.* 4% ($P < 0.0001$)	Overall similar TEAEs incidence in the dupilumab and placebo group (64% *vs.* 74%). No dupilumab-related adverse events were serious or led to treatment discontinuation
Nemolizumab							
NCT03921411	Completed; completion date: August 19, 2020	Phase II, multicenter, OL, single-group study	$n = 20$; aged 12 to 17 years	SC injection of 30 mg nemolizumab Q4W for 16 weeks, a loading dose of 60 mg on Day 1.	PK parameters. Incidence of AEs. IGA score, EASI-75, and PP-NRS	Similar PK of nemolizumab in adolescents and adults. A marked improvement in rash, itch, and sleep. By week 16, a 66.5% improvement of EASI score; 60% achieving EASI-75; 35% achieving IGA score 0 or 1; 50% reduction of SCORAD scores; 43.2% improvement in PP-NRS	33.3% overall; types: eczema, peripheral edema, and staphylococcal skin infection.

(Continues)

TABLE 1 (Continued)

Clinical trials	Status	Study design	Patients (number, age)	Interventions	Primary outcomes measures	Results of primary outcomes	Adverse events
Abrocitinib							
NCT03796676	Completed; completion date: April 8, 2020	Phase III, randomized, DB, multicenter, parallel-group study	$n = 287$; aged 12 to 17 years	Oral intake of 100 mg or 200 mg abrocitinib, or placebo, once daily for 12 weeks	Participants achieving IGA score of 0 or 1 or a reduced score ≥2, and EASI-75 at week 12	Patients with IGA responses: 46.2%, 41.6%, and 24.5% in abrocitinib 200 mg, 100 mg, and placebo groups. Patients with EASI-75 improvement: 72.0%, 68.5% *vs*. 41.5%; $P < 0.05$ for both	AEs: 62.8%, 56.8%, and 52.1% in the 200 mg, 100 mg, and placebo groups, respectively; SAEs: 1.1%, 0, and 2.1% in the 200 mg, 100 mg, and placebo groups, respectively
NCT03575871	Completed; completion date: August 13, 2019	Phase III, randomized, DB, multicenter, parallel-group study	$n = 391$; aged 12 years and older	Oral intake of 100 mg or 200 mg abrocitinib, or placebo, once daily for 12 weeks	Participants achieving IGA score of 0 or 1 or a reduced score ≥2, and EASI-75 at week 12	Patients with IGA responses: 38.1% and 28.4% *vs*. 9.1% in abrocitinib 200 mg, 100 mg, *vs*. placebo groups; $P < 0.001$ for both. Patients with EASI-75 improvement: 61.0%, 44.5% *vs*. 10.4%; $P < 0.001$ for both.	AEs: 65.8%, 62.7%, and 53.8% in the 200 mg, 100 mg, and placebo groups, respectively; SAEs: an 1.3%, 3.2% and 1.3% in the 200 mg, 100 mg, and placebo groups, respectively
NCT03349060	Completed; completion date: March 26, 2019	Phase III, randomized, DB, multicenter, parallel-group study	$n = 387$; aged 12 years and older	Oral intake of 100 mg or 200 mg abrocitinib, or placebo, once daily for 12 weeks	Participants achieving IGA score of 0 or 1 or a reduced score ≥2, and EASI-75 at week 12	Patients with IGA responses: 44%, 24% *vs*. 8% in abrocitinib 200 mg, 100 mg, *vs*. placebo groups, $P < 0.0001$ and $P = 0.0037$. Patients with EASI-75 improvement: 40%, 63% *vs*. 12% in 100 mg 200 mg group, *vs*. 12% placebo groups; $P < 0.0001$ for both.	AEs: 78%, 69%, and 57% in the 200 mg, 100 mg, and placebo groups, respectively; SAEs: a 3%, 3%, and 4% in the 200 mg, 100 mg, and placebo groups, respectively
Upadacitinib							
NCT03569293	Active, not recruiting; estimated completion date: October 9, 2025	Phase III, randomized, OL, parallel-group study	$n = 912$; aged 12 to 75 years	Oral intake of 15 mg or 30 mg upadacitinib, or placebo once daily for 16 weeks; and blinded extension treatment up to week 260	Participants achieving vIGA-AD score of 0 or 1 or a reduced score ≥ 2 at week 16, and proportion of participants achieving EASI-75 at week 16	Patients with vIGA-AD responses: 70%, 80% *vs*. 16% in upadacitinib 15 mg, 30 mg, *vs*. placebo group. Patients with EASI-75 improvement: 48% and 62%, *vs*. 8% in upadacitinib 15 mg, 30 mg, *vs*. placebo group	The incidence of TEAEs was similar between the upadacitinib 15 mg and 30 mg groups, and higher than placebo groups. The rate of treatment discontinuations due to AEs was low overall, and higher in the upadacitinib 30 mg group *vs*. 15 mg group. The most frequently reported TEAEs were acne, upper respiratory tract infection, nasopharyngitis, headache, elevation in plasma creatine phosphokinase levels.
NCT03607422	Active, not recruiting; estimated completion date: December 3, 2025	Phase III, randomized, OL, parallel-group study	$n = 912$; aged 12 to 75 years	Oral intake of 15 mg or 30 mg upadacitinib, or placebo once daily for 16 weeks; and blinded extension treatment up to week 260	Participants achieving vIGA-AD score of 0 or 1 or a reduced score ≥ 2 at week 16, and proportion of participants achieving EASI-75 at week 16	Patients with vIGA-AD responses: 60%, 73% *vs*. 13% in upadacitinib 15 mg, 30 mg, *vs*. placebo group. Patients with EASI-75 improvement: 39% and 52%, *vs*. 5% in upadacitinib 15 mg, 30 mg, *vs*. placebo group	/
NCT03568318	Active, not recruiting; estimated completion date: November 16, 2025	Phase III, randomized, DB, placebo-controlled study	$n = 968$; aged 12 to 75 years	Oral intake of upadacitinib 15 mg plus TCS, upadacitinib 30 mg plus TCS, or placebo plus TCS	Participants achieving vIGA-AD score of 0 or 1 or a reduced score ≥ 2 at week 16, and proportion of participants achieving EASI-75 at week 16	Patients with vIGA-AD responses: 40%, 59% *vs*. 11% in upadacitinib 15 mg, 30 mg, *vs*. placebo plus TCS group. Patients with EASI-75 improvement: 65% and 77%, *vs*. 26% in upadacitinib 15 mg, 30 mg, *vs*. placebo plus TCS group	AE: 67%, 72%, and 63% in upadacitinib 15 mg, 30 mg, *vs*. placebo plus TCS group; SAEs: 1%, 1%, and 2% in upadacitinib 15 mg, 30 mg, *vs*. placebo plus TCS group, respectively.

Abbreviation: OL, open-label; SC, subcutaneous; PK, pharmacokinetics; EASI, eczema area and severity index; EASI-75, EASI ≥ 75% improvement from baseline; TEAEs, treatment-emergent adverse events; SAE, serious adverse events; OLE, open-label extension; DB, double-blind; Q4W, every 4 weeks; Q2W, every 2 weeks; TCS, topical corticosteroids; RCT, randomized controlled study; IGA, investigator global assessment; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; CPT-3, Conners' Continuous Performance Test-3; AE, adverse events; PP-NRS, peak pruritus numeric rating scale; SCORAD, SCORing Atopic Dermatitis; OLE, open-label extension.

LIBERTY AD PEDS (NCT03345914) targeting children aged 6–11 years with severe AD was completed in September 2019.[16] Three hundred and sixty-seven patients were enrolled and randomized 1:1:1 to 300 mg dupilumab Q4W, 100 mg or 200 mg Q2W, or placebo; with concomitant medium-potency topical corticosteroids (TCS). At week 16, significantly more patients receiving dupilumab in combination with TCS achieved the primary endpoints: an IGA score of 0 or 1 (Q2W, 29.5% [$P = 0.0004$]; Q4W, 32.8% [$P < 0.0001$]; placebo, 11.4%) and the EASI-75 (Q2W, 67.2% [$P < 0.0001$]; Q4W, 69.7% [$P < 0.0001$]; placebo, 26.8%). Additional disease symptom measurements also supported its efficacy, including itch, anxiety, depression, sleep, and QoL, with $P < 0.0001$ in all comparisons. The overall incidence of treatment-emergent AEs (TEAEs) was lower in the dupilumab than in placebo groups (65.0%, 67.2% *vs*. 73.3%). Injection-site reactions and conjunctivitis were the only two TEAEs with a higher incidence in dupilumab plus TCS, mostly in mild-to-moderate severity. In conclusion, dupilumab in combination with TCS is supported to be efficacious and well-tolerated in children with severe AD in this clinical trial.[17]

LIBERTY AD PED-OLE is an ongoing phase III, Open-label (OL) trial (NCT02612454) with the enrollment of subjects in previous dupilumab trials including R668-AD-1412 (a phase II study, NCT02407756), LIBERTY AD ADOL and LIBERTY AD PEDS (as mentioned above) and it will be completed in November 2026. Cork et al.[18,19] reported the pharmacokinetics and long-term efficacy of dupilumab in adolescents (aged ≥ 12 years) with moderate-to-severe AD and children (aged 6–12 years) with severe AD from the results of R668-AD-1412 and its subsequent phase III OLE. Patients are administrated with 2 or 4 mg/kg dupilumab weekly. For adolescent patients aged ≥12 years, the pharmacokinetics profile of dupilumab was nonlinear and target-mediated, which was similar to that in adults. By week 52, nearly all adolescents reported one or more TEAEs. Nasopharyngitis (41% and 47% in the 2 and 4 mg/kg group, respectively) and AD exacerbation (29% and 42%) are the most common, and other TEAEs such as skin infections, injection-site reactions, and conjunctivitis, mainly are mild in intensity. Three patients experienced serious adverse events (SAE) (patent ductus arteriosus, food allergy, and ankle fracture), which were not considered related to the study treatment. No TEAEs led to permanent treatment discontinuation.[18] For children aged 6–12 years with uncontrolled severe AD, they achieved rapid and further improvements with mean EASI and peak pruritus numeric rating scales (PP-NRS) improved by −92%/−84% (2 mg/kg) and −70%/−58% (4 mg/kg) at week 52 (OLE), respectively. Nearly all children reported at least one TEAE. TEAEs were mostly mild-to-moderate and transient, mostly nasopharyngitis (47% and 56%, respectively) and AD exacerbation (29% and 13%, respectively). Two patients in the 2 mg/kg dose group (12%) and three patients in the 4 mg/kg dose group (19%) experienced at least one serious TEAE, but none were related to treatment or led to discontinuation of the study drug.[19] These results demonstrated the 52-week safety and efficacy of dupilumab and supported it as a continuous long-term treatment for children aged ≥ 6 years. Based on the results of LIBERTY AD PED-OLE, Blauvelt et al.[20] further put forward the long-term efficacy and acceptable safety of dupilumab for adolescents with a larger sample of 294 participants in 2022. By week 52, 42.7% of patients had an IGA score of 0/1, and 81.2% achieved EASI-75. About 73.8% of patients experienced at least one TEAE, most of which were mild-to-moderate and transient. Eleven patients (3.7%) had severe TEAEs, including patent ductus arteriosus, injection-site edema, food allergy, herpes simplex infection, and ankle fracture. All severe events resolved over time, and none led to treatment discontinuation. They also proposed the Q2W dose regimen as optimal for this age group and the need for continued dupilumab to maintain efficacy.[20]

Pagan et al.[21] carried out a real-world, single-center study by reviewing electronic medical records from March 2017 to September 2021 of moderate-to-severe AD patients starting dupilumab at less than the age of 18 years. Eighty-nine patients were included and their mean treatment duration was 1.3 ± 0.9 years. Among them, all patients ($n = 23$) who received dupilumab for 1 year or more achieved EASI-75 and IGA 0/1. The prevalence of AEs was 13.5%, of which conjunctivitis and joint pain were most common, and no SAE occurred.[21] This real-world study further supported the well-tolerance and efficacy of dupilumab in treating pediatric and adolescent AD regardless of age, sex, race, or ethnicity.

The ongoing clinical trials of dupilumab in pediatric AD

Many dupilumab trials are ongoing to further investigate its efficacy in relieving AD symptoms as well as its long-term safety for adolescents and children. A phase III, randomized, double-blinded study (NCT04678882) aims to evaluate the efficacy and safety of dupilumab concomitantly with TCS in 62 Japanese participants aged 6 months to 18 years.[22] The improvements of AD symptoms such as sleep disturbance and neuropsychology after dupilumab administration are under investigated in two phase IV study (NCT05042258 and NCT05203380), respectively. One focused on the improvement of circadian function, sleep, and pruritus in participants.[23] Another phase IV study is the first one to quantify cognitive deficits in adolescents with moderate-to-severe AD and measure its changes after dupilumab administration by employing Conners' Continuous Performance Test-3 d' T-score as the measurement.[24] For the treatment of dupilumab in moderate-to-severe

atopic hand and foot dermatitis, a phase III trial (Liberty-AD-HAFT, NCT04417894) was carried out in April 2021. One hundred and thirty participants aged 12 years and older will be enrolled in this study and assessed by IGA (hand and foot).[25]

Nemolizumab

Nemolizumab is a humanized monoclonal antibody targeting the IL-31 receptor α (IL-31Rα) subunit. It binds the IL-31 receptor on a spectrum of cells including neurons, which can inhibit the potentiation of the sensation of pruritus. To date, two phase II studies (for 12 and 24 weeks, respectively) of nemolizumab in adults with moderate-to-severe AD have been completed, both reporting significant improvements in cutaneous signs of inflammation and pruritus by monthly subcutaneous injections.[26,27] A 64-week extension study of the 12-week study further showed its efficacy and good tolerance.[28]

The efficacy and safety of nemolizumab in pediatric AD

A phase II, multicenter, open-label, signal-group clinical trial (NCT03921411) assessed the pharmacokinetics and safety of nemolizumab in adolescents ($n = 20$, aged 12-17 years) with moderate-to-severe AD.[29] The administration of subcutaneous nemolizumab started at a loading dose of 60 mg at baseline, followed by 30 mg Q4W until week 12 with background TCS or calcineurin inhibitors. Patients had a marked improvement in rash, itch, and sleep, with decreased scores from baseline to week 16 in EASI by $66.5\% \pm 32.5\%$, in PP-NRS by $43.2\% \pm 37\%$, and in sleep disturbance NRS by $53.5\% \pm 47.8\%$. In addition, the pharmacokinetics profiles of 12- to 17-year-old adolescents in this study were similar to that of adults, with a mean half-life of 16.7 ± 4.1 days. Further evaluation of the relationship between nemolizumab systemic exposure and clinical efficacy endpoints demonstrated similar exposure-response profiles in adolescents and adults for the three clinical endpoints (EASI, IGA, and PP-NRS).[30] AEs were experienced by 33.3% of subjects.[30]

The ongoing clinical trials of nemolizumab in pediatric AD

A phase II trial (NCT04921345) was launched in 2021 to further assess the pharmacokinetics, safety, and efficacy of nemolizumab in pediatric subjects (aged 2 to 11 years) with moderate-to-severe AD.[31] One phase II and three phase III nemolizumab trials are currently underway to assess the efficacy and safety of nemolizumab in patients over the age of 12 years old. The phase II trial (NCT04365387) in subjects ages 12 to 54 years old aims to assess the effect of nemolizumab on humoral immune responses to tetanus and meningococcal vaccination.[32] Two phase III studies (NCT03989349 and NCT03985943) began in June 2019 to assess the efficacy and safety of nemolizumab after a 16-week treatment period in subjects aged 12 years and above.[33,34] The other phase III prospective, multicenter, long-term study with approximately 1700 participants aged 12 years and older began in 2019 and is estimated to conclude in August 2026.[35]

BIOLOGICS TARGETING TYPE 2 CYTOKINES

Tralokinumab

Tralokinumab is an IL-13-neutralising humanized monoclonal IgG4 antibody (MAB), that specifically binds with high affinity to IL-13 helices A and D in epitope, preventing its interaction with both IL-13Rα1 and IL-13Rα2.[36] Based on results from the ECZTRA 1 to 3 trials, tralokinumab has been approved in the European Union and FDA for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy.[37–39]

For tralokinumab administration in adolescents with moderate-to-severe AD, two phase III clinical trials have been conducted, but the results remain unreported. ECZTRA 6 (ECZema TRAlokinumab Trial no. 6, NCT03526861) is a multicenter parallel-group trial to evaluate the safety, immunogenicity, and tolerability of subcutaneous tralokinumab from week 16 to 52 in adolescent subjects.[40] ECZTEND (NCT03587805) is a long-term extension trial, which aims at evaluating the long-term safety of tralokinumab with maintenance dose from week 2 up to week 266.[41]

Targeting the pharmacokinetic and safety of tralokinumab for children under 12 years old, TRAPEDS 1 (TRAlokinumab PEDiatric Trial no. 1, NCT05388760) was recently posted.[42] The primary outcome measures include trough concentration at week 16, as well as maximum plasma concentration (Cmax), time to maximum observed plasma concentration (Tmax), the area under the plasma concentration-time curve (AUC) between week 12 to week 14 for Q2W (week 12–week 16 for Q4W).[42]

Lebrikizumab

Lebrikizumab is a novel MAB that binds with a very high affinity to IL-13 at an epitope that overlaps strongly with the binding site of IL-4Rα, thus preventing the formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex.[43] The efficacy and safety of lebrikizumab in adults with moderate-to-severe AD have been reported in phase IIa proof-of-concept study (TREBLE) and phase IIb dose-ranging trial.[44,45]

Two clinical trials of lebrikizumab in pediatric patients with AD have been completed, but results have not been reported. Adore (NCT04250350) was a phase III study to

assess the safety and efficacy of lebrikizumab in adolescent patients (aged 12–17 years) with moderate-to-severe AD.[46] The primary outcome is the percentage of participants who discontinued from study due to AEs.[46] Aiming at evaluating the efficacy and safety of lebrikizumab in combination with TCS, adhere (NCT04250337, $n = 228$, aged 12 years and older) is a phase III trial with 16-week duration and has been concluded in September 2021.[47]

BIOLOGICS TARGETING IGE

Omalizumab

Omalizumab is the first and only commercially-available anti-IgE antibody. It is a humanized monoclonal antibody that focuses against the constant region of the heavy ε chain of free systemic IgE and inhibits its binding to IgE receptors, thereby limiting mast cell degranulation and inflammatory mediator release.[48] It has been approved for use in patients with persistent allergic asthma in patients aged 6–12 years old and for chronic urticaria in patients aged ≥ 12 years old. It is licensed for use from the age of 6 years, as safety data suggest that omalizumab is well tolerated in children in this age range.[49]

The efficacy and safety of omalizumab in pediatric AD was first evaluated in a phase I study (OXID, NCT01678092) of 8 patients between the ages of 4 and 22 years (mean 11.6 years) with severe refractory AD in 2004.[50] This study showed that patients receiving omalizumab had strikingly decreased levels of cytokines that were involved in Th2 polarization (TSLP and TARC) compared to placebo. But the improvement in clinical outcomes measured by the SCORAD index didn't show efficiency, with a 20%–50% reduction in the omalizumab group compared to a 45%–80% reduction in the placebo group.[51] Lacombe Barrios et al.[52] reported the treatment of omalizumab in seven pediatric patients with severe AD. The clinical improvement was observed with a mean reduction of 45.6 points in the SCORAD index and a mean reduction of 60.5% in total serum IgE levels of all patients and no AEs were reported in the 30-month follow-up. Most recently in the AD anti-IgE pediatric trial (ADAPT, NCT02300701), a 24-week clinical trial that ended in August 2018.[53] Subcutaneous injection of omalizumab or placebo with the dosage based on total IgE and body weight was administered to 62 participants aged 4–19 years with severe eczema.[54] The mean difference in objective SCORAD index improvement after 24 weeks of treatment was -6.9 after adjustment (95% confidence interval, -12.2 to -1.5; $P = 0.01$), significantly favoring omalizumab therapy. Improvements in disease severity and QoL scores were also seen.[54] SAE occurred in each group with similar incidence (20% in omalizumab and 19% in the placebo group).[54]

ORAL SMALL-MOLECULAR INHIBITORS: JAK INHIBITORS

JAK inhibition has emerged as a promising therapeutic approach for AD, targeting JAK-STAT signaling, critical for Th2 cytokines like IL-4, IL-13, and IL-31. Investigations into topical and oral JAK inhibitors in pediatric AD have shown promising results. Ruxolitinib 1.5% cream (a JAK1/2 inhibitor) gained FDA approval in 2021 for mild-to-moderate AD in patients aged 12 years and above.[55] Delgocitinib 0.5% ointment (JAK1/2/3, TYK2 inhibitor) was approved in Japan for patients aged above 16 years with mild-to-moderate AD.[56] A phase IIb study of brepocitinib (JAK1/TYK2 inhibitor) in adolescents and adults was recently completed.[57] In patients with moderate-to-severe AD, oral JAK inhibitors such as baricitinib (JAK1/2), abrocitinib, and upadacitinib (both JAK1-selective) demonstrated efficacy in numerous trials with manageable AEs. JAK inhibitors hold great promise as the next generation of targeted AD therapy. This review highlights systemic therapy, focusing on the latest updates of three oral JAK inhibitors.

Baricitinib

Batricitinib is an oral small-molecule inhibitor of JAK1 and JAK2 that targets inflammatory pathways in AD. It has been approved with a usual dose of 4 mg once a day, followed by a reduced dose of 2 mg once a day under a controlled disease condition in Europe, for moderate-to-severe AD in adults who are candidates for systemic therapy, supported by a series of phase III studies (BREEZE-AD1 to BREEZE-AD6) with 16- or 104-week duration.[58–63] The safety analysis of baricitinib demonstrated a similar low frequency of serious infections, opportunistic infections, and conjunctival disorders between treatment groups (4 or 2 mg once a day), both doses were higher than placebo.[64] Current evidence supported baricitinib as an oral alternative to subcutaneous biologics for the treatment of moderate to severe AD in adults who are candidates for systemic therapy.[65]

The study of baricitinib in the treatment of pediatric AD patients is still underway, BREEZE-AD-PEDS (NCT03952559) is an ongoing, phase III study to evaluate the pharmacokinetics, efficacy, and safety of baricitinib in pediatric patients with moderate-to-severe AD.[66] The primary outcome measures include the percentage of patients achieving IGA 0/1 or a reduction of more than 2, Cmax, and AUC of baricitinib from baseline through 2 weeks. This study is estimated to be completed in January 2027.[66]

Abrocitinib

Abrocitinib is an oral, small-molecule inhibitor of JAK1. Various cytokines relevant to the pathophysiology of AD,

including IL-4, IL-13, IL-22, IL-31, and γ-interferon activate heterodimeric receptors containing JAK1, thereby mediating Th2 cell differentiation and pruritus via downstream effects.[67] JAK2 forms homodimeric receptor complexes and is involved in hematopoiesis.[68] Therefore, selective inhibition of JAK1 is an ideal target to modulate many cytokines involved in the pathogenesis of AD while avoiding the undesirable effects of JAK2 inhibition, such as neutropenia and anemia.[69] In September 2021, abrocitinib was approved in the United Kingdom and Japan for the treatment of adolescents and adults with moderate-to-severe AD aged 12 years and older who are candidates for systemic therapy. In January 2022, Abrocitinib was approved by the FDA for the treatment of adults with refractory, moderate-to-severe AD. Recently in 2023, the approval has been extended for the treatment of adolescents aged 12–18 years old with refractory, moderate-to-severe AD. The recommended dosage is 100 or 200 mg once daily.

The efficacy and safety of abrocitinib in pediatric AD

The treatment of oral abrocitinib has shown positive prospectives in adolescents with moderate-to-severe AD. Two phase III trials, JADE MONO-1 (NCT03349060) and JADE MONO-2 (NCT03575871), have evaluated the efficacy and safety of abrocitinib in adolescents and adults with moderate-to-severe AD.[70,71] In JADE MONO-1, patients were assigned to oral abrocitinib 100 mg, or abrocitinib 200 mg, or placebo for 12 weeks.[71] The primary outcomes showed that significantly more subjects achieved IGA 0/1 (24% in 100 mg group, 44% in 200 mg group, *vs*. 8% in placebo group, $P < 0.005$), as well as EASI-75 (40% in 100 mg group and 63% in 200 mg group, *vs*. 12% in placebo group, $P < 0.0001$). The incidence of SAEs was low (< 4%) in both abrocitinib groups and seemed to be comparable to placebo.[72] With the same regime of abrocitinib, the primary outcomes of JADE MONO-2 also demonstrated significantly greater proportions of patients in the 200 mg and 100 mg abrocitinib groups versus the placebo group achieved IGA responses (38.1% and 28.4% *vs*. 9.1%, $P < 0.001$) and EASI-75 (61.0% and 44.5% *vs*. 10.4%, $P < 0.001$).[70] The AEs were 65.8% in the 200 mg group, 62.7% in the 100 mg group, and 53.8% in the placebo group, while SAEs were reported for 1.3%, 3.2%, and 1.3%, respectively. In all, these two studies supported that monotherapy with oral abrocitinib once daily was effective and well tolerated in adolescents and adults with moderate-to-severe AD.

JADE TEEN (NCT03796676), a multicenter phase III trial, reported the efficacy and safety of abrocitinib in adolescents with moderate-to-severe AD in combination with topical therapy.[73] Two hundred and eighty-five adolescents were randomly assigned 1:1:1 to receive once-daily oral abrocitinib, 200 or 100 mg, or placebo for 12 weeks in combination with topical therapy. IGA responses occurred in 46.2%, 41.6%, and 24.5% of patients respectively, with significant differences between placebo *versus* 200 mg abrocitinib (20.6%, $P < 0.05$), and 100 mg abrocitinib (16.7%, $P < 0.05$).[74] Significant differences in EASI-75 response rates were also reported for 29.4% and 26.5% in placebo *vs*. abrocitinib, 200 and 100 mg ($P < 0.05$ in both groups). The most frequently reported TEAEs were nausea (18.1% in the 200 mg group) and upper respiratory tract infection (10.4% in the 200 mg group) in the abrocitinib group.[74,75] Incidence of AEs that led to study discontinuation were similar or lower in the abrocitinib groups than in placebo (2.1% in the 200 mg group, 1.1% in the 100 mg group, and 2.1% in placebo group), suggesting that combining abrocitinib with topical therapies does not adversely affect the benefit-risk profile in adolescents.[74]

Cork et al.[75] evaluated the impact of abrocitinib on patient-reported symptoms, including sleep loss and QoL among adolescents with moderate-to-severe AD based on the above three studies: JADE TEEN, JADE MONO-1, and JADE MONO-2. They reported that more adolescents treated with abrocitinib (200 or 100 mg) versus placebo achieved a ≥ 4- and ≥ 6-point improvement from baseline in the Patient-Oriented Eczema Measure and Children's Dermatology Life Quality Index in these three studies.[75] Significant improvements in sleep loss scores were also demonstrated with abrocitinib versus placebo at weeks 2-12.[75]

The ongoing clinical trials of abrocitinib in pediatric AD

JADE EXTEND (NCT03422822) is a phase III long-term extension study to investigate the efficacy and safety of abrocitinib with or without topical medications for subjects aged 12 years and older with moderate-to-severe AD.[76] The primary outcome measures include the incidence of TEAEs, SAEs, and AEs leading to discontinuation, change from baseline in clinical laboratory values, and vital signs.[76] Another phase III trial aims to assess the safety and efficacy of orally administered tablets of abrocitinib in participants aged 12 years and older with moderate-to-severe AD in India.[77]

Upadacitinib

Upadacitinib is also an oral, selective, small-molecule JAK inhibitor with greater inhibitory effects for JAK1 than JAK2, JAK3, and TYK2. Recently in January 2022, the FDA approved upadacitinib (15 or 30 mg, orally) for the treatment of adults and children aged 12 years and older with refractory and moderate-to-severe AD, which was based on three multicenter, randomized, double-blinded, placebo-controlled, phase III trials (Measure Up 1, Measure Up 2, and AD Up).

The efficacy and safety of upadacitinib in pediatric AD

Measure Up 1 (NCT03569293) and Measure Up 2 (NCT03607422) were done over 150 clinical centers in over 20 countries with the enrollment of 847 and 836 participants aged 12 years and older respectively.[78,79] Patients were randomly assigned to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo once daily for 16 weeks. The coprimary endpoints were met in both studies (all $P < 0.0001$). In Measure Up 1, significantly more patients achieved EASI-75 at week 16, with 70% in the upadacitinib 15 mg, 80% in the 30 mg, versus 16% in the placebo group. The proportion of patients who achieved a validated IGA (vIGA) response (vIGA score of 0/1 or a reduction from baseline of ≥ 2 points) at week 16 was also significantly higher in the upadacitinib 15 mg and 30 mg group than the placebo group (48% and 62%, *vs*. 8%). The efficacy of upadacitinib was also demonstrated in Measure Up 2, with the proportion of 60% in the 15 mg group and 73% in the 30 mg group, versus 13% in the placebo group achieving EASI-75, and 48%, 62%, versus 8% achieving a vIGA response, respectively. In addition, efficacy at week 16 was maintained during the long-term (52 weeks) follow-up study of Measure Up 1 and Measure Up 2. The proportion of patients achieving EASI-75 were 82.0% and 79.1% of those continuing the 15 mg dose and 84.9% and 84.3% of those continuing the 30 mg dose (for Measure Up 1 and Measure Up 2, respectively); and vIGA response was achieved by 59.2% and 52.6% and 62.5% and 65.1% of patients in the Measure Up 1 and Measure Up 2 studies, respectively, $P < 0.0001$ in all regimes.[80] Both upadacitinib doses were well tolerated. The incidence of SAE and AEs leading to study drug discontinuation were similar among groups. The most frequently reported TEAEs were acne, upper respiratory tract infection, nasopharyngitis, and elevation in creatine phosphokinase levels. Measure Up 1 and Measure Up 2 supported that monotherapy with upadacitinib had a positive benefit-risk profile in adolescents and adults with moderate-to-severe AD.[80,81]

AD Up (NCT03568318) aimed to evaluate the safety and efficacy of upadacitinib in combination with TCS in adolescents and adults with moderate-to-severe AD.[82] Nine hundred and one patients aged 12 years and older were enrolled and randomly assigned to receive upadacitinib 15 mg plus TCS, upadacitinib 30 mg plus TCS, or placebo plus TCS. At week 16, the proportion of patients who had achieved EASI-75 was significantly higher in the upadacitinib 15 and 30 mg plus TCS group than in the placebo group (65% and 77%, *vs*. 26%). Significantly more patients achieved a vIGA response at week 16, with 40% in the upadacitinib 15 mg plus TCS, 59% in the 30 mg plus TCS, *vs*. 11% in the placebo plus TCS group. In addition, upadacitinib 15 mg and 30 mg were well tolerated in combination with TCS. The most three frequent TEAEs were acne, nasopharyngitis, upper respiratory tract infection, and oral herpes. AD Up indicated that upadacitinib as a combination therapy also had a positive benefit-risk profile in adults and adolescents with moderate-to-severe AD.[83]

The ongoing clinical trials of upadacitinib in pediatric AD

A phase 1 multiple-dose study (NCT03646604) was carried out in January 2019 to evaluate the treatment of upadacitinib in pediatric subjects with severe AD.[84] Participants will be assigned to two age groups (2 to 6 and 6 to 12 years old) and received low dose or high dose of upadacitinib orally. The primary outcome measures include Cmax, Tmax, AUC, and oral clearance up to 7 days, and number of participants with TEAEs up to 2 years.[84] A post-marketing observational study (NCT05029895) started in 2021 to evaluate the safety and effectiveness of upadacitinib in adolescent patients aged 12–18 years old with AD in Japan in the real-world setting, with an estimated enrollment of 170 participants.[85] Rising Up (NCT03661138) is a phase 3 study to evaluate the safety of upadacitinib in combination with TCS in adolescent and adult subjects in Japan.[86] Two real-world studies, UP-TAINED (NCT05139836) and ADVISE (NCT05081557) were started in 2022 to assess the effectiveness of oral upadacitinib in adult and adolescent (≥ 12 years old) participants with AD, with an estimated enrollment of 772 and 975 participants respectively.[87,88]

DISCUSSION

Novel biologics are undergoing scrutiny, heralding a departure from conventional immunosuppressive therapies towards innovative treatments. However, the application of novel biologics and small-molecule drugs in pediatric AD patients is a subject of contention. Therefore, we've reviewed the most update clinical trials and studies regarding the efficacy and safety of biologics and oral small-molecule drugs in pediatric patients with AD.

Presently, the most extensively studied biologic in pediatric patients is dupilumab, supported by clinical trials spanning children aged 6 months–18 years. Notably, upadatinib, the pioneering FDA-approved JAK inhibitor, is indicated for adolescents aged 12–18 years; however, its clinical evaluation pertains to those above 12 years, encompassing adolescents and adults, without exclusive data for adolescents. In our analysis, summarized in Table S1, under recommended dosages, upadatinib displayed superior overall efficacy compared to dupilumab. Specifically, the proportion of patients achieving EASI-75 was 38.1%–41.5% for dupilumab versus 60%–84.9% for upadatinib, and IGA0/1 scores were 15.5%–22.0% for dupilumab versus 39%–62% for upadatinib. In the context of safety profiles, the incidence of TEAEs mirrored between dupilumab and upadatinib (63.9%–72.0%

vs. 60.0%–73.0%, respectively). SAE did not necessitate discontinuation in either cohort. Prevalent TEAEs for dupilumab included nasopharyngitis, conjunctivitis, skin infections, and injection-site reactions, primarily of mild intensity. For upadatinib, common TEAEs encompassed acne, upper respiratory tract infections, and nasopharyngitis. However, it should be noted that the results of upadacitinib were based on studies involving both adolescents and adults. For moderate to severe pediatric AD patients under 12 years of age, dupilumab remains the only approved biologic and should be used as first-line treatment. For patients over 12 years old, upadacitinib has also shown good efficacy and reasonable safety. Nevertheless, given the lack of clinical trial data specifically targeting pediatric patients with AD, dupilumab remains the first choice for treatment in pediatric clinics. Future clinical trials on the use of upadacitinib in pediatric AD patients may provide additional support for its use in clinical settings.

Abrocitinib was recently approved by the FDA for the treatment of patients aged 12 years and older with moderate-to-severe AD, with recommended once-daily doses of 100 mg or 200 mg orally. The treatment of 100 or 200 mg abrocitinib combined with topical therapy in adolescents showed significant efficacy similar to that of dupilumab in adolescents. The most frequently reported TEAEs were nausea and upper respiratory tract infection. The serious AEs led to discontinuation happened both in abrocitinib ($n = 1$ [1.1%] in 100 mg group, $n = 2$ [2.1%] in 200 mg group) and placebo group ($n = 2$ [2.1%]). Contrasting with upadacitinib, it is worth noting that abrocitinib lacks extended-release formulations, has a briefer half-life, and primarily undergoes enzymatic metabolism, which may potentially introduce drug interaction considerations. Studies of nemolizumab in adult AD demonstrated its superiority in improving pruritus. In adolescents, a study of 20 participants showed a marked improvement in symptoms with consistent pharmacokinetics with that in adults. However, two participants (an incidence of 10%) discontinued the study due to serious AEs.

Other emerging systemic biologics and small-molecular inhibitors, such as lebrikizumab, tralokinumab, omalizumab, and baricitinib still do not have safety or efficacy data results, as they are currently undergoing phase III trials to evaluate their use in pediatric patients. In the future, large-scale and long-term prospective studies are imperative to further investigate the efficacy of biologics in pediatrics with AD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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