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REVIEW

Modern Interventions for Pediatric Atopic Dermatitis: An Updated Pharmacologic Approach

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ABSTRACT

Pediatric atopic dermatitis (AD) has historically challenged dermatologists given the variable response of patients to treatment and limited available therapeutic options, often with significant potential side effects. Over the last decade, targeted treatments including dupilumab and Janus kinase (JAK) inhibitors have emerged as significant treatment advances. An updated therapeutic approach for incorporating these new practice-changing medications can help clinicians manage these challenging patients. In this review, we discuss emerging topical and systemic (oral and injectable) treatments in pediatric AD, including topical PDE4 inhibitors and tapinarof, oral JAK inhibitors, and injected biologics including IL-4Rα inhibitor dupilumab, IL-13 inhibitor tralokinumab, IL-13Rα inhibitor lebrikizumab, IL-31Rα inhibitor nemolizumab, and IL-5Rα inhibitor benralizumab. We also review experimental agents in early clinical trials, such as targeted microbiome transplant lotions/antimicrobials, which may gain relevance in AD treatment. Finally, we propose a therapeutic approach for pediatric AD that incorporates newer therapies including dupilumab and JAK inhibitors, recognizing that these agents may not be universally available or approved. Further trials that include pediatric patients, especially head-to-head studies among therapeutic classes, are needed to clarify the role of emerging treatments.

Keywords: Atopic dermatitis; Crisaborole; Dupilumab; Pediatric; Ruxolitinib; Upadacitinib

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Key Summary Points

AD pathogenesis is heterogeneous; though T helper 2 (T_H2) inflammation is common to all AD patients, the role of additional immune endotypes with specific potentially targetable cytokines, small molecules, and pruritogens have yet to be fully clarified.

Newly FDA-approved agents for pediatric AD include topical crisaborole (PDE4 inhibitor), topical ruxolitinib (JAK 1/2 inhibitor), oral upadacitinib (JAK 1 selective inhibitor), and injected dupilumab (anti-IL-4/13 monoclonal antibody), though phase 2 and 3 trials support the use of additional topical PDE4 inhibitors and an aryl hydrocarbon receptor agonist (tapinarof), topical and oral JAK inhibitors, and the injectable biologic treatments anti-IL-13 tralokinumab/anti-IL-13Rα lebrikizumab and anti-IL-31Rα nemolizumab in pediatric AD. Many of these medications are not universally available and cost may prohibit use.

Treatment selection for AD in pediatric populations depends on patient age/weight, body surface area affected, medical comorbidities, quality of life, and response to other treatments as well as cost and availability/approval of pharmacologic agents in the locality of the patient.

On the basis of current evidence and whether these medications in the pediatric AD arsenal are available, we recommend an approach of treating mild–moderate AD with topical corticosteroid or a steroid-sparing topical (topical calcineurin inhibitor, PDE4 inhibitor, or JAK inhibitor); dupilumab may be considered for refractory moderate–severe pediatric AD in patients who fail topical or other conventional therapy where it is approved and available. Systemic JAK inhibitors (such as upadacitinib) may be utilized for patients who fail to respond to dupilumab with refractory severe symptoms. The availability and ages of approval for these systemic agents vary across countries. Often concomitant use of topicals and systemic therapies is effective for moderate–severe disease.

Head-to-head trials including pediatric patients are necessary to further elucidate the role of emerging treatments in pediatric AD.

INTRODUCTION

Atopic dermatitis (AD) is a chronic dermatitis affecting 15–20% of children [1]. Though AD pathogenesis is heterogeneous, a "one-size-fits-all" often guides treatment [2]. Topical corticosteroids (TCS) and calcineurin inhibitors (CNIs) are typical first-line agents for mild–moderate AD with subsequent escalation to phototherapy or systemic immunosuppression with cyclosporine, azathioprine, methotrexate, or mycophenolate mofetil for refractory/severe cases [3]. New targeted treatments are now available. These treatments pose a challenge to practicing dermatologists as there are few head-to-head trials to guide treatment decisions. In this review, we discuss new/emerging therapeutics in pediatric AD and propose an updated treatment approach. This

article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The authors acknowledge that therapeutics discussed may not yet be approved for the same age groups in all countries or available in all countries.

Although knowledge of AD pathophysiology is expanding, the multifactorial nature is not fully understood. Barrier dysfunction, genetic factors, immune dysregulation, microbiome dysbiosis, and environmental exposures are implicated. Epidermal barrier disruption by external factors (allergens or irritants) promotes expression of immune alarmins interleukin (IL)-1β, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). IL-1β and IL-33 induce a T helper 2 (T_H2) response with production of IL-4, IL-5, and IL-13 cytokines. These T_H2 cytokines promote further T_H2 polarization [4]. TSLP activates the T_H2 pathway indirectly via stimulation of dendritic cell OX40 ligand (OX40L) expression, which activates T cells by binding OX40. IL-33 and OX40L stimulate production of pruritogenic IL-31. A cyclic inflammatory cascade whereby T_H2 cytokines/chemokines promote further impairment of the epidermal barrier results. T_H2 inflammation further weakens epidermal defenses by downregulating antimicrobial peptide (AMP) in response to environmental organisms, including *Staphylococcus aureus* [1, 5]. The T_H2 activation pathway is common to all patients with AD. Increased T_H17 signaling mediated by IL-36/IL-36 receptor and increased T_H22 cells/IL-22 expression have been described. There is also emerging evidence that specific immune endotypes exist. Increased T_H17 immunity was observed in infants, children, and Asian patients while increased T_H1 immunity was observed in adults, but not pediatric patients [1]. The Janus kinase (JAK) signal transducer and activator of transcription (STAT) signaling pathway is shared by T_H2, T_H17, and T_H1 cytokines. Itch pathways in AD are heterogeneous with potential for endogenous pruritogens (cytokines) or exogenous pruritogens (allergens, irritants, microbes) to stimulate unmyelinated nonhistaminergic dorsal root ganglia C-fiber neurons. IL-31, IL-33, and TSLP are direct pruritogens, while IL-4 and IL-13 indirectly upregulate the dorsal root ganglia signaling response [1, 5].

TOPICAL AGENTS

Traditional topical treatments (TCSs and CNIs) risk potentially significant side effects, and CNIs still carry a black box warning of malignancy despite studies showing long-term safety in infants/children [6, 7]. Additional steroid-sparing agents are needed [8]. There are many topical treatments that completed or are in active trials for pediatric AD (Table 1).

PDE4 Inhibitors

Elevated phosphodiesterase 4 (PDE4) in skin affected by AD results in decreased cyclic adenylate monophosphate (cAMP) levels and resultant increased proinflammatory cytokines. PDE4 inhibitors increase cAMP levels, thereby decreasing proinflammatory cytokines [9].

Crisaborole 2% ointment was the first PDE4 inhibitor studied for AD. Phase 3 randomized double-blind vehicle-controlled trials (RDBVCTs) (CrisADe CORE 1 and CrisADe CORE 2) of patients ≥ 2 years with mild–moderate AD demonstrated improved Investigator's Static Global Assessment (ISGA) 0/1 scores with ≥ 2-grade improvement in 32.8%/31.4% of crisaborole-treated subjects compared with 25.4%/18% vehicle-treated subjects after 28 days [10]. This led to FDA approval for patients ≥ 2 years. A subsequent phase 4 open label (OL) study of infants ≥ 3 months–2 years (CrisADe CARE 1) demonstrated ISGA 0/1 with ≥ 2-grade improvement in 30.2% of patients, resulting in extended FDA approval for infants ≥ 3 months [11]. Application site reactions, though uncommon in original studies, were subsequently demonstrated in 32–50% of patients, with greater rates with facial application [12]. Crisaborole is not approved outside of the USA.

Difamilast is approved in Japan for AD patients ≥ 2 years with similar efficacy to crisaborole with few reports of application site discomfort [9, 13, 14]. There is an active phase 3

Table 1 New and emerging topical treatments

Drug (Target)	Trial identifier	Study type	Subject number	Age	AD severity baseline	Study treatment duration	Primary endpoints	Key secondary endpoints	Adverse events	Status
Crisaborole 2% ointment (PDE4)	NCT02118766, NCT02118792	Parallel phase 3 RDBVCT	759, 763	≥ 2 years	Mild–mod	28 days	ISGA 0/1 (met)	Itch scores (met)	Application site pain	FDA approved age ≥ 2 years
	NCT03356977	Phase 4 OL	137	3 to < 24 months	Mild–mod	28 days	Safety (met)	ISGA 0/1, EASI score, POEM (met)	Application site pain/ discomfort/ erythema	FDA approved age ≥ 3 months
Difamilast ointment (PDE4)	NCT02068352	Phase 2 RDBVCT	121	10 years–70 years	Mild–mod	8 weeks	IGA 0/1 (met)	IGA, EASI, VAS pruritus (met)	AD flare (in 0.3% difamilast), pruritus	Completed
	NCT03018691	Phase 2 RDBVCT, parallel group	73	2–14 years	Mild–mod	4 weeks	Safety (met)	IGA 0/1, EASI, VAS/ VRS pruritus, POEM, %BSA (met)	Infrequent folliculitis	Completed
	NCT03911401	Phase 3 RDBVCT	251	2–14 years	Mild–mod	4 weeks	IGA 0/1 + ≥ 2 grade improvement (met)	EASI, VRS pruritus, POEM, BSA (met)	Infrequent folliculitis and impetigo	Approved in Japan age ≥ 2 years
Roflumilast cream (PDE4)	NCT04773587	Phase 3 RDBVCT	654	≥ 6 years	Not specified	4 weeks	IGA 0/1 + ≥ 2 grade improvement	EASI-75, Itch NRS	NA	Completed, results not reported
	NCT04773600	Phase 3 RDBVCT, parallel group	683	≥ 6 years	Not specified	4 weeks	IGA 0/1 + ≥ 2 grade improvement	EASI-75, Itch NRS	NA	Active, not recruiting

Table 1 continued

Drug (Target)	Trial identifier	Study type	Subject number	Age	AD severity baseline	Study treatment duration	Primary endpoints	Key secondary endpoints	Adverse events	Status
	NCT04845620	Phase 3 RDBVCT, parallel group	650 (estimated)	2–5 years	Not specified	4 weeks	IGA 0/1 + ≥ 2 grade improvement	EASI-75	NA	Active, recruiting
Tapinarof cream (AHR)	NCT02564055	Phase 2b RDBVCT	247	12–65 years	Moderate–severe	12 weeks	IGA 0/1 + ≥ 2 grade improvement (met)	EASI-75, Itch NRS, %BSA (met)	Mild folliculitis	Completed
	NCT05014568	Phase 3 RDBVCT	400 (estimated)	≥ 2 years	Moderate-Severe	8 weeks	IGA 0/1	EASI-75/ EASI-90, Itch NRS, % BSA	NA	Active, recruiting
	NCT05032859	Phase 3 RDBVCT	400 (estimated)	≥ 2 years	Moderate–severe	8 weeks	IGA 0/1	EASI-75/ EASI-90, Itch NRS, %BSA	NA	Active, recruiting
	NCT05142774	Phase 3 OL	961 (estimated)	2 to < 18 years	Moderate–severe	48 weeks	Safety	IGA, % BSA, EASI-50/ 75/90, peak pruritus (PP)-NRS	NA	Active, recruiting
Ruxolitinib cream (JAK 1 and 2)	NCT03745638, NCT03745651	Phase 3 RDBVCT	631, 618	≥ 12 years	Mild–moderate	52 weeks (8 + 44 extension)	IGA 0/1 + ≥ 2 grade improvement (met)	EASI-75, Itch NRS (met)	Nasopharyngitis, URTI, headache	Completed
	NCT04921969	Phase 3 RDBVCT	250 (estimated)	2–11 years	Mild–moderate	52 weeks (8 + 44 extension)	IGA 0/1 + ≥ 2 grade improvement	EASI-75, Itch NRS	NA	Recruiting

Table 1 continued

Drug (Target)	Trial identifier	Study type	Subject number	Age	AD severity baseline	Study treatment duration	Primary endpoints	Key secondary endpoints	Adverse events	Status
Delgocitinib ointment/cream (Pan JAK)	JapicCTI-173554	Phase 3	158	2–15 years		28 weeks (4 weeks + 24 open label extension)	%mEASI	mEASI-50/75, IGA 0/1, itch NRS,	Impetigo, nasopharyngitis, urticaria	Complete
	JapicCTI-173555	Phase 3	352	≥ 16 years		52 weeks	Safety	%mEASI, mEASI-75, IGA 0/1, % I-NRS	Acne, eczema herpeticum, nasopharyngitis	Complete
	JapicCTI-184064	Phase 3 RDBVCT		2–15 years	Mild–severe	52 weeks	%mEASI	mEASI-50/75, IGA 0/1, pruritus score	Folliculitis, acne, nasopharyngitis, influenza, impetigo, eczema herpeticum (favored unrelated)	Approved Japan
Brepocitinib cream (JAK1/TYK2)	NCT 03,903,822	Phase 2b RDBVCT	240	12–75 years	Mild–moderate	6 weeks	%EASI (all except 0.1% and 0.3% bid met)	EASI-75 (only 0.3% bid, 1% bid), IGA 0/1 (all except 1% qd, 0.3% qd, 0.1% qd), PP-NRS (all except 0.2%, 0.3%)	Nasopharyngitis, URTI, folliculitis, furuncle, herpes simplex, eczema herpeticum	Completed

ISGA Investigator's Static Global Assessment, *IGA* Investigator's Global Assessment, *ISGA0/1 or IGA 0/1* skin clear or almost clear + ≥ 2 grade improvement, *EASI* Eczema Area and Severity Index, *EASI-50/75/90* improvement of ≥ 50%/75%/90% in EASI, *POEM* patient-oriented eczema measure, *VAS* visual analog scale, *VRS* verbal rating scale, *BSA* body surface area, *% BSA* percent change in body surface area, *NRS* numerical rating scale, *%mEASI* percent improvement in modified EASI

trial (NCT05372653) evaluating difamilast in infants ≥ 3 months–2 years.

Roflumilast (ARQ-151) failed to demonstrate a significant SCORing Atopic Dermatitis (SCORAD) improvement, but improved itch in a phase 2a adult trial [15]. One phase 3 RDBVCT of roflumilast including patients ≥ 6 years (INTEGUMENT I) was completed (NCT04773587), and additional phase 3 trials are active (NCT04773600, NCT04845620).

BOX 1: CRISABOROLE

Practical results of our authors' experience with crisaborole suggests limited uptake due to minimal responses and localized discomfort at sites of application. Take caution before prescribing crisaborole for facial use given increased risk of discomfort at this site. Difamilast is not yet approved in the USA, but may prove beneficial given the lack of burning sensation associated with crisaborole. Crisaborole use is limited geographically as it is not approved outside the USA.

Aryl Hydrocarbon

Tapinarof is a small molecule aryl hydrocarbon receptor (AHR) agonist. When activated, the AhR/AhR nuclear translocator (ARNT) system promotes increased keratinocyte barrier gene expression [16]. The AhR/ARNT system decreases T_H2 cytokines, oxidative stress, and is implicated in immunoregulation [17, 18]. A phase 2b RDBVCT in adolescents reported improved IGA 0/1 (53% versus 24%), Eczema Area and Severity Index (EASI) (60% versus 26%), and itch scores (30% versus 5%) in tapinarof versus vehicle [8]. Folliculitis and acne were reported [19]. Tapinarof has advanced to phase 3 trials that will include patients ≥ 2 years (NCT05014568, NCT05032859, NCT05142774).

BOX 2: TAPINAROF

Tapinarof is already on the market (FDA approved for psoriasis) and may be available for AD soon. Benefits include lack of burning sensation and few reported application site reactions. Watch for allergic contact dermatitis as this was reported in psoriasis trials [20].

JAK INHIBITORS

Topical JAK

The JAK family is composed of four cytoplasmatic tyrosine kinases: JAK1, JAK2, JAK3, and tyrosine kinase-2 (TYK2). Linked to transmembrane receptors, JAKs potentiate intracellular signaling of inflammatory mediators (interleukins/interferons) via STAT proteins [21, 22]. JAK phosphorylation causes STAT separation, dimerization, and translocation to the nucleus, where they induce gene transcription integral to immunity, proliferation, apoptosis, and differentiation [23]. Current understanding of AD emphasizes the role of T_H2 IL-4, IL-5, IL-13, IL-31 and Th22 (IL-22) immune responses [24]. The JAK–STAT pathway mediates binding of key cytokines to promote inflammation and itch [4]. JAK1 is particularly important for T_H2 cytokine signaling [25, 26]. Multiple JAK inhibitors have completed or are in active trials (Tables 1 and 2).

Topical ruxolitinib (RUX) 1.5% is a JAK1/2 selective inhibitor. Two phase 3 trials (TRuE-AD1/AD2) in patients ≥ 12 years with mild–moderate AD demonstrated improvement in IGA 0/1 (54%/51% versus 15%/8%), higher rates of EASI-75 (62%/62% versus 25%/14%), and improved pruritus including itch reduction within 12 h of first application in RUX versus vehicle [27]. Results of TRuE-AD led to FDA approval in patients ≥ 12 years old in 2021. Notably, approval is limited to ≤ 20% BSA for 8 weeks. A subsequent phase 1 OL trial of RUX 1.5% cream revealed two patients of greater BSA involvement (45% and 90%) that exceeded the half maximal inhibitory concentration for JAK-mediated myelosuppression [28]. This study revealed potential benefit with use of topical

Table 2 New and emerging oral treatments

Drug (Target)	Trial ID	Study type	Subject number	Age	Study treatment duration	Primary endpoint	Key secondary endpoints	Adverse events	Status
Upadacitinib (JAK1)	NCT03569293, NCT03607422	Replicate phase 3 RDBPCT (Measure Up 1 and Measure Up 2)	847, 836	12–75 years	16 weeks	EASI-75, vIGA-AD 0/1 (met)	WP-NRS4, EASI, ADerm-IS, ADerm-SS	Acne, URTI, nasopharyngitis, headache	FDA approved ages 12+, 2021
	NCT03568318	Parallel phase 3 RDBPCT (AD Up)	968	12–75 years	16 weeks + blinded extension (up to week 260)	EASI-75, vIGA-AD 0/1	WP-NRS4, EASI	Nasopharyngitis, acne, and URTI	Active, not recruiting
Abrocitinib (JAK1)	NCT03349060, NCT03575871	Parallel phase 3 RDBPCT (JADE MONO 1 and 2)	387, 391	≥ 12 years	12 weeks	IGA 0/1, EASI-75 (met)	PP-NRS4, PSAAD (met)	Nausea, vomiting, headache, acne, transient low platelets, elevated CPK, LDL/HDL	Completed
	NCT03796676	Parallel phase 3 RDBPCT (JADE TEEN)	285	12–17 years	12 weeks	IGA 0/1, EASI-75 (met)	PP-NRS4, PSAAD	Nausea, vomiting, headache, acne, transient low platelets, elevated CPK, LDL/HDL	Completed
Baricitinib (JAK 1 and 2)	NCT03952559	Phase 3 RDBPCT (BREEZE-AD-PEDS)	465 (estimated)	2–17 years	16 weeks	IGA 0/1, PK	EASI, SCORAD, NRS4, PRISM, POEM, PGI-S-AD, CDLQI/IDQOL, WPAI-AD-CG, EQ-5D-Y, ADSS	NA	Recruiting

EASI Eczema Area and Severity Index, *EASI-75* improvement of ≥ 75% in EASI, *vIGA-AD* Validated Investigator's Global Assessment, *WP-NRS4* Worst Pruritus Numerical Rating Scale, *ADerm-IS* Atopic Dermatitis Impact Scale, *ADerm-SS* Atopic Dermatitis Symptom Scale, *IGA 0/1* 0/1 skin clear or almost clear + ≥ 2 grade improvement, *PSAAD* Pruritus and Symptoms Assessment for Atopic Dermatitis, *SCORAD* Scoring Atopic Dermatitis (scoring index); *NRS4* ≥ 4 point improvement in numerical rating scale, *PRISM* Parent-Reported Itch Severity Measure, *POEM* patient-oriented eczema measure, *PGI-S-AD* Patient Global Impression of Severity–Atopic Dermatitis, *CDLQI/IDQOL* Children's/Infants' Dermatology Life Quality Index, *WPAI-AD-CG* Work Productivity and Activity Impairment: Atopic Dermatitis-Caregiver, *EQ-5D-Y* European Quality of Life-5 Dimensions-Youth, *ADSS* atopic dermatitis sleep scale

RUX for higher % BSA, but demonstrated a risk of systemic absorption. Further research is needed to determine the upper limit of safe % BSA use. A phase 3 RDBVCT in children (TRuE-AD3) is recruiting (NCT04921969). Patients have found topical RUX to be an effective alternative with almost no reports of stinging/burning. Cost is the greatest hurdle to use.

Delgocitinib (DELGO) is a pan-JAK (JAK1/2/3 and TYK2) inhibitor approved in Japan for patients ≥ 2 years [29, 30]. Approval was based on a phase 3 RDBVCT in patients 2–15 years that demonstrated a decrease in the least squares mean percent change in modified EASI score with delgocitinib (−39.3% DELGO versus +10.9% vehicle) [31]. A phase 3 trial of patients ≥ 6–24 months was completed and topline results are positive [32]. In the USA, a phase 1 trial of delgocitinib was completed and included patients ≥ 2 years. Results are not available (NCT03826901), and there are no further active trials. Both topical RUX and delgocitinib are associated with minimal side effects. In the delgocitinib trials, two cases of eczema herpeticum were reported.

Topical brepocitinib (JAK1/TYK2) cream was evaluated in a phase 2 trial of adolescent patients ≥ 12 years (NCT03903822). In this study, patients using 1% brepocitinib cream once daily had an average decrease in their EASI score of −70%, compared with −44% using vehicle cream. Patients using 1% brepocitinib cream twice daily had an average decrease in their EASI score of −75%, compared with −48% using vehicle cream. Tofacitinib ointment (JAK 1/3, NCT 02,001,181, completed 2020) and ATI-502 solution (JAK 1/3, NCT03585296, completed 2021) completed phase 2 trials in adults, but do not have further trials at this time.

BOX 3: TOPICAL JAK INHIBITORS

Topical JAK inhibitors have a reasonable safety profile and are not associated with application site burning/stinging. Use of topical JAK inhibitors is limited by approval for only limited BSA involvement (≤ 20%) and cost.

Oral JAK

JAK inhibitors have emerged as the first available oral targeted treatments for AD. Upadacitinib is a JAK1-selective inhibitor FDA approved for refractory moderate–severe AD in patients ≥ 12 years. In two phase 3 RDBPCTs (Measure Up 1 and 2) including patients ≥ 12 years, significant improvements in EASI-75 (80%/73% versus 70%/60% versus 16%/13%), validated IGA 0/1 (62%/52% versus 48%/39% versus 8%/5%), and itch scores were reported in upadacitinib 30 mg and 15 mg arms compared with placebo [33]. A phase 3b head-to-head trial (Heads Up) comparing 30 mg upadacitinib to dupilumab (DUPI) in adults showed slightly better improvement in EASI-75 scores in upadacitinib (71%) versus DUPI (61%) and significant improvement in pruritus score [34]. A phase 3 RDBPCT (AD Up) evaluating upadacitinib in combination with TCSs in patients 12–75 years reported improved EASI-75 (77% versus 65% versus 26%) and validated IGA-AD 0/1 (59% versus 40% versus 11%) in upadacitinib 30 mg versus 15 mg versus placebo, respectively (NCT03568318). This trial is now in a prolonged extension phase. A phase 1 OL study in children ages 2–12 years with severe AD is ongoing (NCT03646604).

Abrocitinib is a JAK1-selective inhibitor FDA approved for refractory moderate–severe AD in adults, but not adolescents. Safety and efficacy of abrocitinib were evaluated in two 12-week phase 3 RDBPCTs of subjects ≥ 12 years old with moderate–severe AD in JADE MONO-1 and JADE MONO-2 [35, 36]. Study arms abrocitinib 200 mg daily versus 100 mg daily versus placebo achieved IGA 0/1 (MONO 1: 43.8% versus 23.7% versus 7.9%; MONO 2: 38.1% versus 28.4% versus 9.1%) and EASI75 (MONO 1: 62.7% versus 39.7% versus 11.8%; MONO 2: 61.0% versus 44.5% versus 10.4%) by week 12. Subjects also achieved improvement in itch scores with abrocitinib compared with placebo. An additional phase 3 trial in adolescents evaluated abrocitinib + topical therapy (JADE-TEEN) [37]. Significant improvements in IGA (IGA 0/1: 46.2% versus 41.6% versus 24.5%), EASI-75 (72.0% versus 68.5% versus 41.5%), and itch scores were met in abrocitinib 200 mg and

100 mg versus placebo, respectively. A dose–response effect was stronger in JADE MONO-1 and MONO-2 compared with JADE-TEEN, possibly due to the concomitant topical therapy in JADE-TEEN. A phase 3 head-to-head trial of abrocitinib versus DUPI was completed in adults (JADE COMPARE) with a significant finding of decreased itch at week 2 in the 200 mg abrocitinib group compared with dupilumab. Otherwise abrocitinib was not noted to differ significantly from DUPI at week 16 [38]. An extension study (JADE EXTEND) of adult patients that had been randomized to the DUPI arm of JADE COMPARE demonstrated sustained response in patients who already responded to DUPI, and clinical benefit with skin clearance and itch relief in many patients who had failed to respond to DUPI [39]. Further studies are needed in pediatric patients, but these results suggest a role for oral JAK inhibitors in patients with AD refractory to DUPI. Similar treatment-emergent adverse events were noted in trials for upadacitinib and abrocitinib, including acne, headaches, herpes virus, upper respiratory infections, and nausea. Lab abnormalities were noted including transient thrombocytopenia, increased creatinine phosphokinase (CPK), and lipid levels, suggesting a role for lab monitoring. Serious adverse events (thromboembolic events and malignancy) were not noted, though long-term studies are needed to determine risk over time.

Baricitinib is approved in Europe for moderate–severe AD in adults on the basis of the results of three phase 3 trials (NCT0333439, NCT03334422, NCT03435081). Two identical phase 3 trials (BREEZE-AD1 and BREEZE-AD2) of adults with moderate–severe AD in Europe, Asia, Latin America, and Australia demonstrated dose-dependent improvement in IGA, EASI score, and itch [40]. This response was again demonstrated in a phase 3 trial (BREEZE-AD5) of adults with moderate–severe AD in North America [41]. Changes in serum CPK and platelets were noted in these studies, but were transient.

BOX 4: ORAL JAK INHIBITORS

Oral JAKs further expand options for patients who are needle-averse or unresponsive to other therapies, including topicals/biologics. Pruritus seems to respond quickly to JAK inhibitors (within 24 h of first dose). Side effects, including risk of nausea and acne, as well as more serious black box warnings, including infection, thrombosis, malignancy, and myelosuppression, should be thoroughly discussed with patients prior to JAK treatment. Lab monitoring is supported by abnormalities in CPK, lipid levels, LFTs, and CBC noted in studies, and testing should be completed before and during treatment per guidelines.

BIOLOGICS

Dupilumab

Dupilumab (DUPI) is the only FDA-approved biologic for pediatric AD. This humanized monoclonal antibody (mAb) binds to IL-4 receptor α (IL-4Rα), blocking IL-4/IL-13 signaling as the IL-4Rα chain is common to both IL-4R complexes: type 1 (IL-4Rα/γc; IL-4 specific) and type 2 (IL-4Rα/IL-13Rα1; IL-4 and IL-13 specific) [4]. Additional biologic agents are in trials (Table 3). Initially approved for adults, approval was expanded to include adolescents ≥ 12 years in March 2019 on the basis of the phase 3 RDBPCT (LIBERTY AD ADOL) [42, 43]. In this trial, more subjects achieved IGA0/1 (24% versus 2%), EASI75 (42% versus 8%), and reduction ≥ 4 in Peak Pruritus NRS (37% versus 5%) in the DUPI arm versus placebo, respectively [44]. The LIBERTY AD PEDS phase 3 RDBPCT of children age 6–11 years with severe AD evaluated DUPI + TCS versus placebo + TCS. More subjects achieved IGA0/1 (33% versus 30% versus 11%), EASI-75 (70% versus 67% versus 27%), and reduction by ≥ 4 of Peak Itch NRS (51% versus 58% versus 12%) in the DUPI every 4-week and 2-week regimen compared with placebo, respectively [45]. These results prompted expanded approval to ≥ 6 years old in 2020 [46]. Evaluating DUPI in subjects ≥ 6 months to < 6 years, the LIBERTY AD PRESCHOOL phase 2 results

Table 3 New and emerging biologic treatments

Drug and target	Study type and trial identifier	Subject number and ages included	AD severity baseline	Study treatment duration	Primary endpoint	Key secondary endpoints	Adverse events	Status
Dupilumab IL-4Rα	Phase 3 RDBPCT (LIBERTY AD ADOL) NCT03054428	251, 12–17 years	Mod–severe	16 weeks	IGA 0/1, EASI-75 (met)	EASI, NRS, % BSA, SCORAD, CDLQI, POEM	Conjunctivitis, injection site reactions	FDA approved age ≥ 12 years 2019
	Phase 3 RDBPCT (LIBERTY AD PEDS) NCT03345914	367, 6–11 years	Severe	16 weeks	IGA 0/1, EASI-75 (met)	EASI-75, %EASI, itch score, %BSA, SCORAD, CDLQI, POEM, DFI, PROMIS, TEAE, mean weekly TCS use	Injection site reactions, conjunctivitis	FDA approved age 6–11 years 2020
	Part A- Phase 2 Part B- Phase 3 RDBPCT (LIBERTY AD PRESCHOOL) NCT03346434	202, ≥ 6 months to 6 years	Mod–severe	Part A- 4 weeks Part B- 16 weeks	Part A- PK, safety Part B- IGA0/1, EASI-75 (met)	Part A- EASI, SCORAD, IGA0/1 Part B- EASI, NRS, %BSA, POEM, SCORAD, DFI, CDLQI, IDQOL	Nasopharyngitis, molluscum contagiosum, viral gastroenteritis, rhinorrhea, dental caries, conjunctivitis	FDA approved age ≥ 6 months to 5 years June 2022
	Phase 3 OL extension study (LIBERTY AD PED-OLE) NCT02612454	880, 6 months to 17 years	Mod–severe	272 weeks	Safety, PK	IGA 0/1, EASI, BSA, SCORAD, CDLQI, IDQOL	Nasopharyngitis, URTI, AD, conjunctivitis	Active, not recruiting
Tralokinumab IL-13	Phase 3 RDBPCT (ECZTRA), NCT02612454	301, 12–17 years	Mod–severe	52 weeks	IGA0/1, EASI-75	Itch NRS, SCORAD, CDLQI, EASI, POEM, pK	Viral URTI, conjunctivitis, headache, injection site reaction	Completed
	Phase 3, OL, extension study (ECZTEND) NCT03587805	1672, ≥ 12 years		266 weeks	Safety	IGA0/1, EASI75	NA	Active, not recruiting
	Phase 3, OL, single arm (INJECZTRA) NCT05194540	120 (estimated), ≥ 12 years	Mod–severe	16 weeks	IGA 0/1, EASI-75	Safety, treatment-emergent anti-drug antibodies	NA	Recruiting

Table 3 continued

Drug and target	Study type and trial identifier	Subject number and ages included	AD severity baseline	Study treatment duration	Primary endpoint	Key secondary endpoints	Adverse events	Status
	Phase 2, single-blinded, randomized, parallel group (TRAPEDS 1), NCT05388760	53, 2–11 years	Mod–severe	52 weeks	PK	Safety, anti-drug antibodies, SCORAD, POEM, EASI	NA	Recruiting
Lebrikizumab IL-13	Phase 3 RDBPCT (Advocate 1), NCT04146363	424, ≥ 12 years	Mod–severe	52 weeks	IGA 0/1, EASI-75	IGA 0/1, itch NRS, EASI, % BSA, DLQI, sleep loss score, PROMIS	Conjunctivitis, injection site reactions, nasopharyngitis	Completed
	Phase 3 RDBPCT (Advocate 2), NCT04178967	445, ≥ 12 years	Mod–severe	52 weeks	IGA 0/1, EASI-75	IGA 0/1, itch NRS, EASI, % BSA, DLQI, sleep loss score, PROMIS	Conjunctivitis, injection site reaction, nasopharyngitis, headache, nausea	Completed
	Phase 3 RDBPCT (Adhere), NCT04250337	228, ≥ 12 years	Mod–severe	16 weeks	IGA 0/1, EASI-75	EASI, itch NRS, % BSA, sleep loss score, SCORAD, CDLQI	Headache, conjunctivitis	Completed
	Phase 3, OL, single arm (Adore), NCT04250350	206, 12–17 years	Mod–severe	52 weeks	Safety	IGA 0/1, EASI, % BSA, PROMIS, CDLQI, PK	NA	Completed, results not published
	Phase 3 RDBPCT (Adhere-J), NCT04760314	280, ≥ 12 years	Mod–severe	16 weeks	IGA 0/1, EASI-75	EASI, itch NRS	NA	Active, not recruiting
	Phase 3 parallel assignment (Adjoin), NCT04392154	1000, ≥ 12 years	Mod–severe	100 weeks	Safety	IGA 0/1, EASI-75	NA	Recruiting
	Phase 3 RDBPCT, NCT05149313	312, ≥ 12 years	Mod–severe	52 weeks	EASI-75	IGA, itch NRS, % BSA, SCORAD, CDLQI	NA	Recruiting
	Phase 3 OL, NCT05369403	120, ≥ 12 years	Mod–severe	24 weeks	EASI-75	IGA 0/1, EASI, itch NRS, sleep loss scale, skin pain NRS, CDLQI, SCORAD	NA	Not yet recruiting
	Phase 3 OL, NCT05372419	80, ≥ 12 years	Mod–severe	24 weeks	EASI-75	IGA 0/1, EASI, itch NRS, sleep loss scale, skin pain NRS, CDLQI, SCORAD	NA	Not yet recruiting

Table 3 continued

Drug and target	Study type and trial identifier	Subject number and ages included	AD severity baseline	Study treatment duration	Primary endpoint	Key secondary endpoints	Adverse events	Status
Nemolizumab IL-31Rα	Two phase 3, long-term, JapicCTI-173740, JapicCTI-183894	215, 88, ≥ 13 years	Mod–severe	52 weeks	pruritus VAS, itch NRS, EASI, sIGA, ISI	DLQI, POEM, mean quantity of topical agents	Nasopharyngitis, AD, inc CPK, contact derm, influenza, urticaria, acne	Completed
	Phase 2 OL, NCT04921345	70, 2–12 years	Mod–severe	52 weeks	PK	EASI, IGA, BSA, PP-NRS, sleep disturbance NRS, cDLQI/iDLQI, POEM	NA	Recruiting
	Phase 2 OL, NCT03921411	20, 12–17 years	Mod–severe	24 weeks	PK, safety			Completed, results not published
	Phase 3 RDBPCT, NCT03985943	750, ≥ 12 years	Mod–severe	16 weeks	IGA 0/1, EASI-75	PP-NRS	NA	Active, not recruiting
	Phase 3 RDBPCT, NCT03989349	750, ≥ 12 years	Mod–severe	16 weeks	IGA 0/1, EASI-75	PP-NRS	NA	Active, not recruiting
	Phase 3, long-term, NCT03989206	1700, ≥ 12 years	Mod–severe	200 weeks	Safety	IGA 0/1, EASI-75, SCORAD, DLQI, POEM	NA	Recruiting
Benralizumab IL-5Rα	Phase 2 RDBPCT, NCT04605094	194, ≥ 12 years	Mod-severe	16 weeks (+ 36-week extension)	IGA 0/1	EASI-75/90, serum anti-drug antibody, peak pruritus score, DLQI and CDLQI	NA	Active, not recruiting

IGA Investigator's Global Assessment, *IGA 0/1* skin clear or almost clear + ≥ 2 grade improvement, *EASI* Eczema Area and Severity Index, *EASI-75* improvement of ≥ 75% in EASI, *NRS* numerical rating scale, *% BSA* percent change in body surface area, *SCORAD* Scoring Atopic Dermatitis (scoring index), *CDLQI/IDQOL* Children's/Infants' Dermatology Life Quality Index, *POEM* patient-oriented eczema measure, *%EASI* percent improvement from baseline in EASI, *DFI* Dermatitis Family Index, *PROMIS* Patient-Reported Outcomes Measurements Information Systems, *TEAE* treatment emergent adverse event

characterized appropriate DUPI safety/pharmacokinetics, and the phase 3 RDBPCT evaluating DUPI + TCS versus placebo + TCS found significantly more patients achieved IGA0/1 (28% versus 4%) and EASI75 (53% versus 11%) with DUPI versus placebo [48, 49]. A significant improvement in itch was also noted with DUPI [47]. This trial led to expanded FDA approval for children ≥ 6 months to 5 years in June 2022 [48]. Dupilumab-related adverse events included conjunctivitis, transient eosinophilia, and injection site reactions [44, 45, 47, 49, 50]. A phase 3 OL extension trial (LIBERTY AD PED-OLE) of patients ≥ 6 months is ongoing (NCT 02,612,454). Results from adolescent patients were recently published with findings relevant for a long-term safety profile consistent with the adult safety profile. Additionally, trial participants with clear/almost clear skin for 12 weeks were discontinued on DUPI with 56.7%, demonstrating recurrence and need to resume DUPI treatment to maintain AD control, which suggests a need to continue DUPI treatment to maintain efficacy [51]. With an excellent safety profile and high response rates, DUPI has become first line, when available, in refractory moderate–severe eczema. Head-to-head trials with JAK inhibitors are helping distinguish the role for these treatments, and further head-to-head trials against other biologics will be needed [34].

BOX 5: DUPILUMAB

Now approved for patients as young as 6 months, DUPI has a great safety profile with the benefit of no required lab monitoring. Administration via injection may limit use in needle-averse patients. DUPI associated conjunctivitis can often be managed with eye drops.

Tralokinumab

IL-13 may play a greater role in peripheral T_H2 inflammation than IL-4. This led to emergence of IL-13 inhibitors for AD treatment [52]. Tralokinumab is an IgG4 mAb that binds to IL-13, preventing activation of the receptor. It was approved for adults with moderate–severe AD in early 2022 after proving safety/efficacy in ECZTRA 1 and ECZTRA 2 phase 3 trials [53]. Adverse events were similar to DUPI [54]. A RDBPCT of tralokinumab monotherapy in adolescents (ECZTRA 6) demonstrated improved IGA and EASI-75 versus placebo (NCT03526861). Additional pediatric trials are active (NCT03587805, NCT05388760).

BOX 6: TRALOKINUMAB

Not yet broadly available for pediatric patients, tralokinumab is FDA approved for adults with AD. The recent ECZTRA 6 trial may lead to FDA approval for adolescents soon. IL-13 inhibitor safety/efficacy appears similar to DUPI. It is unclear if there will be a unique role for IL-13 inhibitors compared with DUPI.

Lebrikizumab

Lebrikizumab is a mAb that inhibits IL-13 signaling by blocking IL-13Rα. A phase 2b trial in adults demonstrated dose-dependent improvement in EASI, IGA0/1, and itch. A total of 12 patients who failed to respond to previous DUPI treatment were randomized to receive lebrikizumab. Five of these 12 achieved EASI-75 at week 16 [55]. Several phase 3 trials including adolescents met primary endpoints (NCT04146363, NCT04178967, NCT04250337) with further active and planned phase 3 trials (NCT04760314, NCT04392154, NCT05149313, NCT05369403, NCT05372419).

BOX 7: LEBRIKIZUMAB

IL-13Rα inhibitors may be as effective as IL-13 inhibitors. Several phase 3 trials that included adolescents met primary endpoints for improvement in AD. Like IL-13 inhibitors, it remains unclear if there is a unique role for IL-13Rα inhibitors compared with DUPI.

Nemolizumab

IL-31 is a pruritogenic cytokine involved in AD pathogenesis. Nemolizumab is an anti-IL-31 receptor α-chain (IL-31Rα) mAb that has shown promising results in phase 2/3 adult trials. Reduced itch in particular was noted, with a lesser improvement in dermatitis [56]. Two recent phase 3 long-term studies in Japanese adolescents demonstrated improved itch with a durable response. Improved EASI, sleep, and life quality were noted by week 16 and persisted through end of treatment [57]. IL-31 expression is increased in children, and nemolizumab may have greater efficacy in this population [56]. Ongoing phase 2/3 trials in adolescents and children are forthcoming (NCT03921411, NCT04921345, NCT03985943, NCT03989349, NCT03989206).

BOX 8: NEMOLIZUMAB

Nemolizumab has demonstrated greater effect on pruritus than dermatitis in AD. Trials are ongoing in pediatric patients. The role of nemolizumab in AD treatment remains unclear.

Benralizumab

Upregulated T_H2 cytokines in AD include IL-5, which promotes eosinophil activation and IgE production. Benralizumab is a mAb targeting IL-5 receptor α chain (IL-5Rα). A phase 2 RDBPCT in adults was completed (NCT03563066) and a phase 2 trial in adolescents is ongoing (NCT04605094).

BOX 9: BENRALIZUMAB

Benralizumab is in early trials. Pending further studies, benralizumab (like DUPI and lebrikizumab) may have a role in treatment of hypereosinophilic-syndrome-associated AD [58].

OTHER EXPERIMENTAL AGENTS

Microbial

Therapeutics targeting cutaneous dysbiosis have yielded mixed results. Omiganan, an antimicrobial peptide, demonstrated recovered dysbiosis in a phase 2 RDBVCT, but did not improve AD [59]. *Roseomonas mucosa* phase 1/2 trials demonstrated improved SCORAD, EASI, and pruritus scores, reduced *S. aureus* burden, and decreased TCS requirements [60, 61]. Targeted microbiome transplant (TMT) lotion containing *Staphylococcus hominis* demonstrated decreased *S. aureus* burden but did not improve dermatitis in a phase 1 trial. However, post hoc analysis of participants with *S. aureus* killed by *S. hominis* demonstrated improved eczema severity [62].

Orals

Oral small molecule inhibitors SCD-044 [sphingosine-1-P (S1P) receptor agonist] and RPT193 [chemokine receptor type 4 (CCR4) antagonist] completed adult trials but have not advanced to pediatric patients (NCT04684485 and NCT05399368).

Injectables

Anti-IgE mAb omalizumab was tested in a RDBPCT (ADAPT) that included pediatric patients with improved SCORAD and quality of life score compared with placebo [63]. There are no further active trials. OX40-targeting biologics completed phase 2 trials in adults, but have not advanced to pediatric populations (NCT03703102, NCT03568162, NCT03754309, NCT05131477). A trial of IL-36 inhibitor, spesolimab infusion, was completed (NCT03822832) in adults. Ustekinumab completed phase 2 trials in adults (NCT01806662, NCT01806662) and did not advance to further testing.

Table 4 FDA-approved treatments for pediatric atopic dermatitis

Drug	Target	Route	Dosing	Boxed warning	Price, USD	Lab monitoring	Special/practical consideration
Tacrolimus	CNI	Topical	Children ≥ 2 years 0.03% ointment twice daily Adolescents ≥ 16 years 0.1% ointment twice daily	Black box warning regarding risk of malignancy (lymphoma and skin) and recommend against use in children < 2 years	$2.80–$11.59 per gram (generic versus brand)	NA	Burning sensation at sites of application may limit use
Pimecrolimus	CNI	Topical	Children ≥ 2 years and adolescents 1% cream twice daily	Black box warning regarding risk of malignancy (lymphoma and skin) and recommend against use in children < 2 years	$10.15–11.96 per gram (generic versus brand)	NA	Less local burning sensation than tacrolimus
Crisaborole	PDE4	Topical	Infants ≥ 3 months, children, and adolescents 2% ointment twice daily	NA	$13.84 per gram	NA	Burning/stinging, especially when used on face
Ruxolitinib	JAK1/2	Topical	Children ≥ 12 years and adolescents 1.5% cream twice daily	Black box warning regarding serious infections (herpes zoster and opportunistic), mortality, malignancies (lymphoma and others), MACE, thrombosis	$39 per gram	CBC as clinically indicated	Approval for use is limited to no more than 20% BSA twice a day for 8 weeks

Table 4 continued

Drug	Target	Route	Dosing	Boxed warning	Price, USD	Lab monitoring	Special/practical consideration
Dupilumab	IL-4/13	Injection	Infants ≥ 6 months to children < 6 years: weight-based dosing using prefilled syringes every 4 weeks; 5 to < 15 kg inject 200 mg q4 weeks, 15 to < 30 kg inject 300 mg q4 weeks Children ≥ 6 years and adolescents < 18 years: weight-based dosing using prefilled syringe (age ≥ 6 years) or prefilled pen (age ≥ 12 years); 15 to < 30 kg inject 600 mg once followed by 300 mg q4 weeks, 30 to < 60 kg inject 400 mg once followed by 200 mg q2 weeks, ≥ 60 kg inject 600 mg once followed by 300 mg q2 weeks	NA	$1015–$2030 per mL	NA	Loading dose not necessary in children < 6 years Often need to fail topical treatments (± phototherapy) prior to insurance approval

Table 4 continued

Drug	Target	Route	Dosing	Boxed warning	Price, USD	Lab monitoring	Special/practical consideration
Upadacitinib	JAK1	Oral	Children ≥ 12 years and adolescents weighing ≥ 40 kg: 15 mg orally once daily (may increase to 30 mg once daily if response inadequate)	Black box warning regarding serious infections (TB, invasive fungal, bacterial, viral including herpes zoster, other opportunistic pathogens), mortality, malignancies (lymphoma and others), MACE, thrombosis	$226 per pill	Prior to treatment: viral hepatitis serologies, TB screen, pregnancy test Baseline and periodically: CBC with differential (monitoring lymphocytes, neutrophils, hemoglobin) LFTs, lipids 12 weeks after initiation and periodically during treatment	Check medication interactions as there are multiple potential interactions Animal studies suggest fetal harm in cases of in utero exposure; unclear risk in humans

APPROACH TO TREATMENT

Many new therapeutic modalities have emerged since the last published American Academy of Dermatology AD guidelines in 2013–2014, including JAK inhibitors and DUPI. New European guidelines include both JAK inhibitors and DUPI for age > 6 years in addition to older systemic agents like azathioprine, methotrexate, and ciclosporin/cyclosporine for children and adolescents with severe disease [64]. On the basis of current evidence, new European guidelines, and expert consensus [64, 65], our authors propose the following approach to treating pediatric patients with AD. Initial therapy should begin with topical treatments that include TCS and steroid-sparing agents. Options for steroid-sparing topicals are now expanded beyond calcineurin inhibitors (tacrolimus or pimecrolimus) to include PDE4 inhibitors (crisaborole, available in the USA) and a topical JAK inhibitor (ruxolitinib, available in the USA, and delgocitinib, available in Japan). Selection of a topical steroid or steroid-sparing agent should be based on BSA involvement, body location of AD, age of the patient, and accessibility for the patient (cost, local country approval, and availability) (See Table 4 for FDA-approved treatments). Often times, topical agents/therapies still play a role in patients with moderate-to-severe atopic dermatitis who are on systemic therapy. The authors do not have space to discuss these in detail. In cases of moderate–severe AD in which systemic treatment is necessary, DUPI can be included as a newer option (in those > 6 years old in Europe and other parts of the world and in those > 6 months in the USA). Conventional systemic medications, including ciclosporin/cyclosporine, methotrexate, and azathioprine, may still be considered on the basis of age, local approval, availability, and cost. For those patients who fail DUPI and/or these other conventional systemic therapies, oral JAK inhibitors may be an additional therapeutic option in older children [39]. Upadacitinib is the oral JAK inhibitor approved by the FDA and European

Medicines Agency (EMA) in pediatric patients age ≥ 12 years. Other treatment options are in development, but further studies are needed in pediatric populations to determine safety/efficacy in these patients. Additionally, head-to-head trials against DUPI are needed to clarify the role of emerging systemic treatments for moderate-to-severe AD.

CONCLUSIONS

As the pathomechanisms and immunologic profiles of AD are better understood, treatment tailored to specific immune endotypes may become the norm, especially when cost and accessibility improve. Though we have not reached this level of personalized medicine in pediatric AD, the approval of DUPI and JAK inhibitors for many age groups have already changed the treatment landscape of pediatric AD. Access to conventional therapies including cyclosporine, methotrexate, topical therapies (steroids, calcineurin inhibitors, and others), and light therapy still play a role for many of those living with atopic dermatitis. Additional systemic and biologic agents are in trials. Inclusion of pediatric patients in these trials, especially head-to-head trials, will be necessary to improve strength of guidelines for pediatric AD treatment choice in the future.

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