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Review

New treatments in atopic dermatitis

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Key Messages

- For decades, treatment of atopic dermatitis (AD) has been limited to topical corticosteroids, topical calcineurin inhibitors, and for those with moderate-to-severe AD, phototherapy and systemic immunosuppressants.
- Despite medical need for more aggressive management, many patients are undertreated owing to concerns about the adverse effects and frequent laboratory monitoring associated with systemic immunosuppressants. Even adherence to topical regimens is threatened by caregiver phobia about the use of topical corticosteroids and calcineurin inhibitors.
- Of note, the following 2 targeted therapies have recently been approved by the US Food and Drug Administration for treatment of AD: topical crisaborole 2% ointment, a phosphodiesterase 4 inhibitor, and subcutaneously injected dupilumab, a monoclonal antibody targeting the interleukin-4 receptor.
- Given the recent advances in our understanding of AD pathogenesis, numerous topical and systemic targeted therapies are in development and likely to alter the landscape of therapeutic options for AD.

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ABSTRACT

Objective: To discuss the efficacy and safety of novel and emerging topical and systemic therapeutic agents for atopic dermatitis (AD).

Data Sources: The review of the published literature was performed using the PubMed database, published abstracts and virtual presentations from scientific meetings, posted results on [ClinicalTrials.gov](https://clinicaltrials.gov), and data from industry press releases.

Study Selection: Primary manuscripts with trial results, case reports, case series, clinical trial data from [ClinicalTrials.gov](https://clinicaltrials.gov), and articles highlighting expert perspectives on management of AD were selected.

Results: Emerging topical and systemic therapies primarily target the type 2 immune pathway. Moreover, 2 newer targeted medications are now approved by the Food and Drug Administration for both children and adults, crisaborole 2% ointment and dupilumab, with several others in the therapeutic pipeline. New directions in developing topical medications include Janus kinase inhibitors, tapinarof (an aryl hydrocarbon receptor agonist), and agents to correct microbial dysbiosis. In addition to the subcutaneously injected monoclonal antibody targeting the interleukin (IL) 4 receptor (dupilumab), other biologics targeting IL-13, IL-31, IL-33, OX40, and thymic stromal lymphopoietin are currently being tested. Oral Janus kinase inhibitors are showing outstanding efficacy and no serious safety signs, but safety concerns remain.

Conclusion: Given the tremendous burden of AD on physical, mental, and social health, the need is high to develop new, targeted therapies. Advances in our understanding of AD pathogenesis have paved the way toward the development of new therapies that promise to revolutionize our management of AD. Future

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research will focus on long-term efficacy and safety and creating predictive models for choosing best management options on a personalized basis.

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory cutaneous disease characterized by pruritus and clinical heterogeneity with regard to age of onset, lesion morphology, distribution and severity of lesions, and long-term persistence. The estimated prevalence of AD is 15% to 20% in children and 7% to 10% in adults.^{1,2} It is associated with skin pain, sleep disturbance, other atopic disorders (allergic rhinoconjunctivitis, food allergy, asthma, and eosinophilic esophagitis), and poor quality of life.³

Although most patients with mild-to-moderate AD respond well to topical corticosteroids (TCS),⁴ there remains an unmet need for topical agents, given safety concerns about TCS use for AD, especially on sensitive skin, such as the face, and the black box warning for topical calcineurin inhibitors, despite growing evidence from long-term studies to dispute the theoretical risk of malignancy.⁵ For patients with moderate-to-severe AD, systemic corticosteroids have been the only systemic agents approved by the Food and Drug Administration (FDA), despite their many long-term safety concerns and tendency to cause rebound when discontinued. As steroid alternatives, phototherapy (often infeasible or poorly tolerated) and immunosuppressants, such as cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine, have been prescribed off-label.⁶ The use of these agents is limited by safety risks, the need for frequent laboratory monitoring, and variable therapeutic benefits.⁶ Our rapidly increasing understanding of the pathogenesis of AD is facilitating the development of more targeted topical and systemic medications that promise to be more efficacious and safer than currently available topical and systemic interventions.

The AD pathogenesis is multifactorial and involves an interplay of epidermal barrier dysfunction, immunologic abnormalities, host genetics, and environmental factors (Fig 1). The outermost layers of the epidermis, the stratum corneum and tight junctions in the stratum granulosum, form a protein and lipid barrier that prevents transepidermal water loss, invasion by microbial pathogens, and inflammation from allergens, toxins, and irritants.^{7,8} In AD, the barrier is impaired, with decreased expression of proteins of epidermal differentiation (particularly filaggrin) and tight junctions and a deficiency of lipids, particularly long-chain fatty acids and ceramides. The barrier against microbes is also diminished by an inadequate antimicrobial peptide (AMP) response to environmental pathogens, including *Staphylococcus aureus*.⁹

In addition to these barrier defects, AD is characterized by cutaneous immune skewing, which forms the basis for most of the new targeted therapeutic approaches. The AD lesions have a cellular infiltrate of primarily CD4⁺ T cells, which are the primary drivers of inflammation, and increased numbers of dendritic cells, including Langerhans cells, which extend their dendrites through tight junctions for antigen uptake. Perturbation of keratinocytes, including by scratching and environmental triggers, leads to keratinocyte release of chemokines, such as CCL17/thymus and activation regulated chemokine and CCL22/macrophage-derived chemokine, and alarmins, such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-1 β , IL-25, and IL-33.⁸ These mediators activate skin-resident type 2 innate lymphoid cells and T_H2 cells to produce the key inflammatory cytokines of AD, IL-13 and IL-4. The TSLP also induces dendritic cells to express the OX40 ligand, which binds to OX40 on T cells to further stimulate IL-4, IL-5, IL-13, and the itch-specific cytokine, IL-31. The IL-36 subfamily and its receptor

IL-36R are expressed in skin (and bronchial epithelium) and are increased in AD, although not to the extent of the increased expression in plaque and pustular psoriasis. *S aureus* is a recognized trigger of cutaneous IL-36 α and IL-36 γ , which activate T_H17 signaling and its amplification.

Increased cutaneous expression of T_H2 cytokines and chemokines is universal in patients with AD and directly promotes tissue inflammation, impairs the epidermal barrier by suppressing expression of proteins of differentiation and lipid synthesis, and suppresses the expression of AMPs in response to organisms.⁸ An increase in T_H22 cells or IL-22 expression is also a consistent finding that is thought to contribute to epidermal hyperproliferation.¹⁰ Upregulation of other helper T cell pathways is heterogeneous and has been linked to certain patient populations, such as increases in T_H1 immunity in adults, but not in Blacks or children, and increases in T_H17 immunity in infants, children, and patients of Asian descent.¹¹ These various immune signaling pathways involved in AD share activation of Janus kinase (JAK) and signal transducer and activator of transcription (STAT).

Patients with AD tend to be colonized with *S aureus* on lesional skin and, to a lesser extent, on nonlesional skin and nasal mucosa. Disease flares are accompanied by relative increases in the abundance of *S aureus* with concurrent reduction in microbial diversity (dysbiosis).¹² This reduction in commensal organisms with direct *S aureus* killing capability and increase in *S aureus* exacerbates the T_H2 response and disease severity.¹³

Itch in AD is sensed primarily by unmyelinated, C-fiber sensory neurons of the dorsal root ganglia (Fig 2). Exogenous pruritogens from the external environment (eg, allergens, pathogens, toxins, irritants) and endogenous pruritogens released from keratinocytes and immune cells (eg, cytokines, lipids, neuropeptides, proteases) bind to and activate a variety of receptors on itch sensory neurons, including cytokine receptors, G-protein coupled receptors, and transient receptor potential (TRP) channels. Activation of these receptors results in the generation of action potentials and local production of mediators of neurogenic inflammation, such as calcitonin gene-related peptide and substance P.¹⁴ In addition to their role in causing inflammation, type 2 cytokines (IL-31, IL-33, and TSLP) can directly activate itch sensory neurons by binding to their cognate receptors on neurons and signaling through the JAK-STAT pathway. Activation of the IL-4 receptor alpha (IL-4R α) on neurons is also JAK-STAT dependent but amplifies the response of neurons to type 2 cytokine pruritogens rather than directly causing itch.¹⁵ As such, targeting these alarmins, T_H2 cytokines, or their receptors may both reduce inflammation and suppress the itch of AD.

New and Emerging Agents

In the past few years, topical crisaborole cream and subcutaneously injected dupilumab have come on the market for use for mild-to-moderate and moderate-to-severe AD in children and adults. In addition, there are many emerging agents described that are topical agents (Table 1), systemically administered monoclonal antibodies (Table 2), or systemically administered small-molecule inhibitors (Table 3).

Topical Agents

Phosphodiesterase 4 Inhibitors

Phosphodiesterase 4 (PDE4) inhibitors increase the reduced levels of cyclic adenosine monophosphate of AD and thereby reduce expression of proinflammatory cytokines. A total of 2 pivotal phase 3, 28-day, randomized, double-blind, vehicle-controlled trials (RDBVCTs) for mild-to-moderate AD of crisaborole 2% ointment, the first topical PDE4 inhibitor, revealed a reduction in the primary end point, the Investigator's Static Global Assessment score to clear (0) or almost clear (1) with a greater than or equal to 2 grade improvement at day 29, in 32.8% and 31.4% of crisaborole-treated patients vs. 25.4% and 18% of vehicle-treated subjects, respectively.¹⁶ Local reactions (pain, burning, and stinging) were uncommon adverse events (AEs), but a subsequent real-world retrospective study suggested that application site pain occurred

overall in 32% of patients, including 50% of those using it for the face.^{16,17} A subsequent phase 4 open-label study of 137 infants 3 to less than 24 months with mild-to-moderate AD revealed crisaborole ointment to achieve the end point of the Investigator's Static Global Assessment in 30.2% of the patients with a safety profile similar to that in older children.¹⁸ Crisaborole 2% ointment was approved by the FDA in 2016 for treatment of mild-to-moderate AD in children 2 years and older, with the indication extended in March 2020 to infants 3 months of age and older.

The PDE4 inhibitor OPA-15406 is in a phase 3 clinical trial (NCT03961529); 1% OPA-15406 achieved IGA0/1 at week 4 (20.9% vs 2.7% with vehicle in adults and 40% vs 8.3% in children).¹⁹ Other topical PDE4 inhibitors, including roflumilast 0.5% cream (NCT01856764), E6005,²⁰ DRM02,²¹ and LEO29102 (NCT01037881), failed to reveal significant benefit ($P < .05$) vs vehicle in phase 1 and 2 clinical trials. However, a phase 1 trial of 0.15% roflumilast

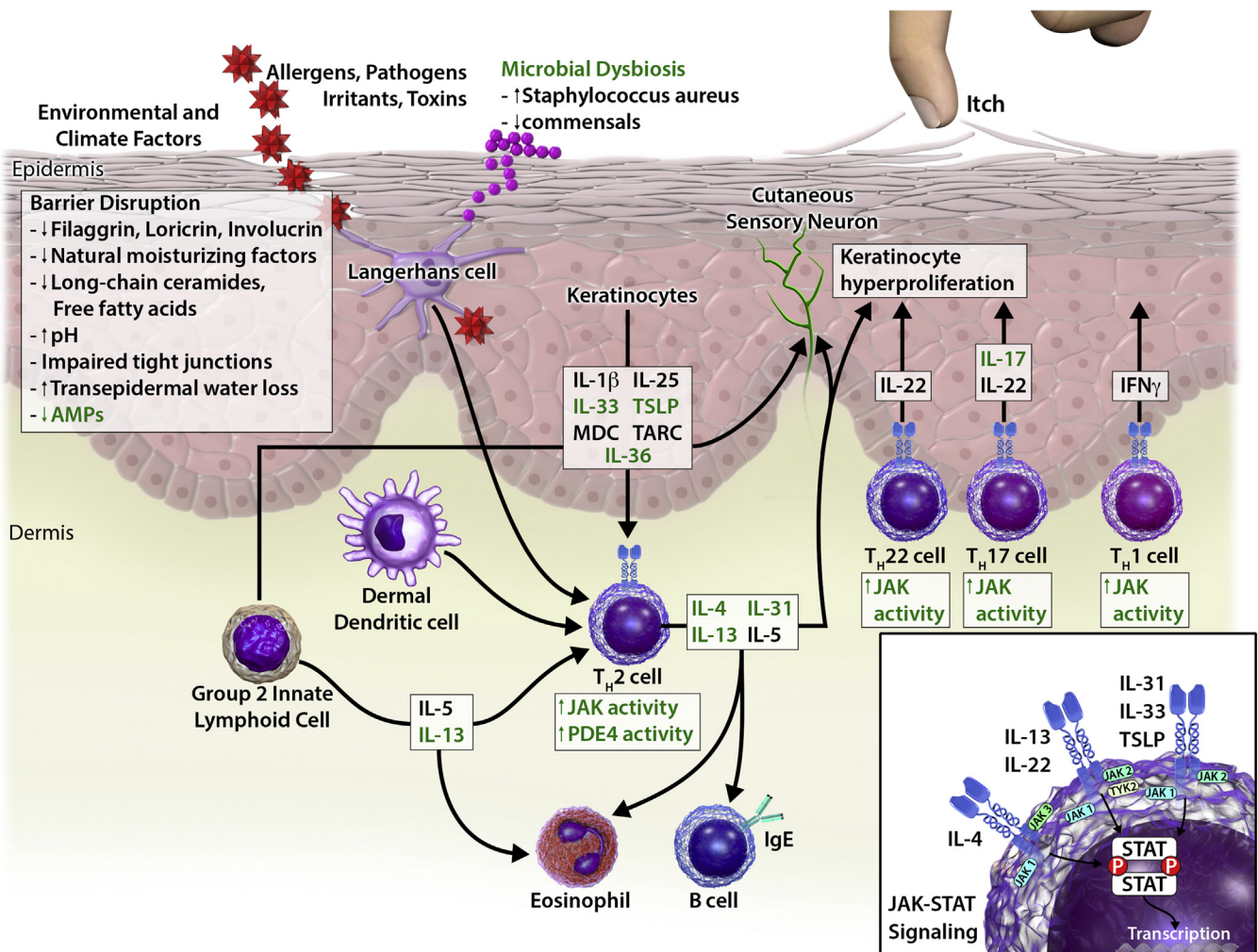


Figure 1. Pathogenesis of atopic dermatitis: immune system targets. The epidermis is composed of both immune and nonimmune structural elements that provide a critical barrier for protection against allergens, pathogens, toxins, and irritants and for maintenance of skin hydration. Atopic dermatitis results from dysregulation of these components. Disrupted epidermal barrier function, resulting in increased susceptibility to external insults and increased transepidermal water loss, and immune dysregulation in both the innate and adaptive immune systems (eg, antimicrobial peptides, cytokines, lymphocytes, and other immune cells) contribute to a chronic inflammatory response. Antigen-presenting cells (Langerhans cells, inflammatory dendritic epidermal cells, dermal dendritic cells) and keratinocytes orchestrate the early stages of inflammation upon encountering allergens and other exogenous and endogenous signals. Keratinocyte-produced IL-25, IL-33, IL-36 and TSLP respond to environmental stimuli, including *S aureus* bacteria, to drive the production of proinflammatory mediators. The resulting type 2 inflammatory response is dominated by T_H2 cell activity and group 2 innate lymphoid cells. Cytokines, particularly IL-13, and IL-4 contribute to barrier dysfunction, altered antimicrobial responses, B-cell IgE class switching, and eosinophil recruitment. Cytokine IL-31 is a key mediator of itch, driven by its binding to IL-31 receptors on itch sensory neurons of the dorsal root ganglion and potentiated by IL-4 and IL-13. Increases in IL-22 (produced mainly by T_H22 cells) drive keratinocyte hyperproliferation, whereas increases in T_H17 and T_H1 cell activities are highly variable, based on age and race/ethnicity. The green print highlights targets of novel and emerging therapies. AMP, antimicrobial peptide; IFN, interferon; Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; PDE4, phosphodiesterase 4; STAT, signal transducer and activator of transcription; T_H, T-helper cells; TSLP, thymic stromal lymphopoietin.

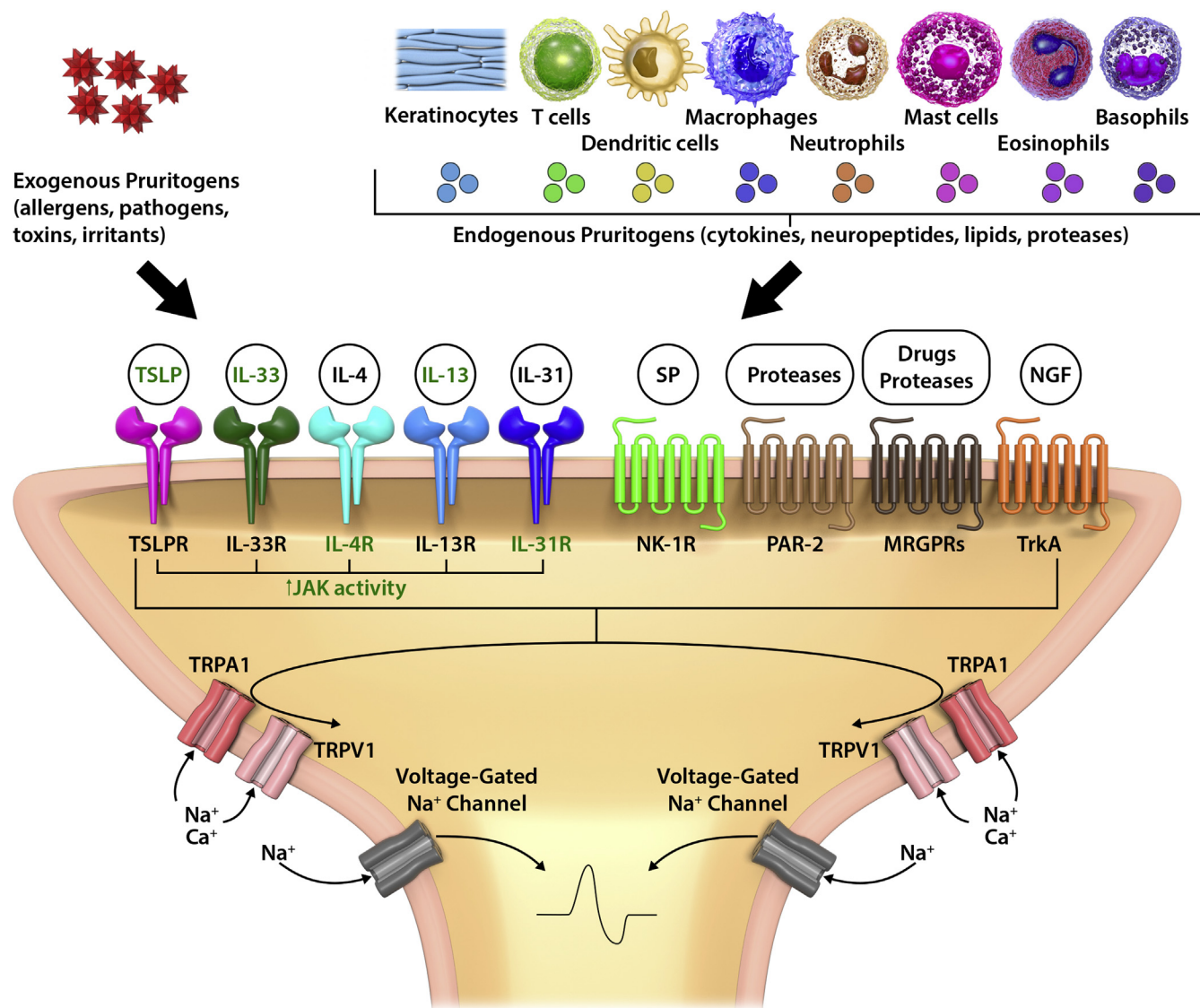


Figure 2. Cutaneous itch sensation in atopic dermatitis: a new focus for finding new targets. Exogenous pruritogens (eg, allergens, pathogens, toxins, and other irritants, such as proteases) from the external environment and endogenous pruritogens (eg, cytokines, neuropeptides, signaling lipids, and proteases) released from keratinocytes and immune cells bind to various receptors on cutaneous itch sensory neurons. Comprised mostly of unmyelinated C-fibers, these sensory neurons signal the itch sensation (as action potentials) to specific dorsal root ganglia and then the central nervous system. Nonhistaminergic, itch-sensitive C-fibers are most important for the itch sensation in atopic dermatitis and are activated by pruritogens, including cytokines (IL-4, IL-13, IL-31, IL-33, TSLP), SP, proteases, circulating drugs, and neurotrophic factors (eg, NGF). Binding of a mediator to its respective receptor results in a secondary messenger signaling cascade, which activates the TRP family of cation channels (especially TRPA and TRPV) and ultimately leads to activation of voltage-gated sodium channels and neuronal depolarization. The TRP channels can also be directly activated by a variety of exogenous and endogenous stimuli (eg, noxious chemicals, temperature, extracellular pH, reactive oxygen species, eicosanoids). Activated C-fibers themselves produce local inflammatory mediators, including SP and calcitonin gene-related peptide. The green print highlights targets of novel and emerging therapies. Ca²⁺, calcium ion; IL, interleukin; JAK, Janus kinase; Na⁺, sodium ion; NGF, nerve growth factor; NK, natural killer; PAR-2, protease activated receptor 2; R, receptor; SP, substance P; TRP, transient receptor potential; TrkA, tropomyosin receptor kinase A; TRPV1, transient receptor potential cation channel subfamily V member 1; TSLP, thymic stromal lymphopoietin.

(ARQ-151) in children and adolescents with mild-to-moderate AD is ongoing (NCT04156191).

Topical Janus Kinase Inhibitors

Cytokines implicated in the pathogenesis of AD, such as IL-4, IL-13, and IL-31, signal through the JAK-STAT pathway and share activation of JAK1, suggesting the value of JAK (and particularly JAK1) inhibition in therapy. A 4-week, phase 2a RDBVCT in adults with mild-to-moderate AD of a topical formulation of tofacitinib, commercially available as an oral JAK 1/3 inhibitor, led to an 82% reduction in the Eczema Area and Severity Index (EASI) score for those treated with topical tofacitinib compared with a 30% reduction in those treated with placebo.²² Improvement in itch was

noted as early as 2 days after initiation, likely by means of blockade of IL-31 signaling. Application site reactions were more frequent with vehicle, unlike the risk from other nonsteroidal topical therapies, such as topical calcineurin inhibitor and crisaborole 2% ointment.²²

In a dose-ranging, randomized, vehicle- and triamcinolone cream-controlled phase 2b trial, adults with mild-to-moderate AD experienced significant reductions in Investigator Global Assessment by greater than or equal to 2 grades to clear or almost clear (IGA0/1), EASI, and itch (by day 2) with twice daily ruxolitinib 1.5% cream (JAK1/2 inhibitor) vs vehicle by week 4 of the 8-week trial. At week 4, significantly more patients in the 1.5% ruxolitinib group achieved IGA 0/1 compared with triamcinolone 0.1% cream (38.0%

Table 1
New and Emerging Topical Agents

	Target	Study type	Study duration	AD severity	Age	Primary end point	Other key end points	Adverse events	Status	Trial identifier
Crisaborole 2% ointment	PDE4	Parallel phase 3, multicenter RDBVCT	28 d	Mild/mod	≥2 y	ISGA0/1: met	Itch (4-point): met	Application site pain	FDA approved for age ≥3 mo	NCT02118766 NCT02118792
		Phase 4, multicenter OL	28 d		3–<24 mo	Safety: met	POEM: met			NCT03356977
OPA-15406	PDE4	Phase 2, multicenter RDBVCT, 3 arm, parallel group	8 wk	Mild/mod	10–70 y	Safety, IGA0/1: met	%EASI, pruritus VAS: met	Mild; infrequent local reactions	Completed	NCT02068352
		Phase 2, multicenter RDBVCT, parallel group	4 wk	n/a	2–14 y	Safety: met	%EASI, IGA0/1, pruritus VAS, POEM: met	Infrequent folliculitis	Completed	NCT03018691
JAK inhibitors										
Ruxolitinib cream	JAK 1/2	Phase 2, RTBVCT, TAC cream-controlled	12 wk	Mild/mod	18–70 y	%EASI: met	IGA0/1, itch NRS: met	Acne	Completed	NCT03011892
		2 Phase 3 RDBVCT	52 wk		≥12 y	IGA0/1: met	EASI75, itch NRS: met			NCT03745638 NCT03745651
Delgocitinib 0.5% ointment	JAK 1/2/3, TYK2	Phase 3, RDBVCT and OL LTE	28 wk	Mod/sev	≥16 y	%mEASI: met	IGA0/1, itch NRS, %BSA: met	Mild; possible eczema herpeticum	Completed	In Japan
ATI-502	JAK 1/3	Phase 2a, multicenter, OL study	8 wk	Mild/sev	≥18 y	Safety: met	Itch (subject pruritus assessment), PGA: met	None	Completed	NCT03585296
Others										
Tapinarof cream (first TAMA)	AHR	Phase 2b, RDBVCT, dose-finding	12 wk	Mod/sev	12–65 y	IGA: met	EASI75, EASI90, %BSA, itch NRS: met	Mild; folliculitis	Completed	NCT02564055
Omigaman gel	AMP	Phase 2, RDBPCT	28 d	Mild/mod	18–65 y	%SCORAD, %BSA, itch VAS: met	None	None	Completed	NCT02456480
TMT lotion (<i>S. hominis</i>)	Commensal bacteria	Phase 1/2, RDBVCT	7 d	Mod/sev	18–60 y	Safety: met	None	None	Completed	NCT03151148
<i>Roseomonas mucosa</i>	Commensal bacteria	Phase 1/2 OL	Adult: 6 wk Pediatric: 16 wk	Mild/sev	3–99 y	asSCORAD50, safety: met	Itch (from SCORAD): met	None	Completed	NCT03018275

Abbreviations: AHR, aryl hydrocarbon receptor; AMP, antimicrobial peptide; asSCORAD, antecubital-specific SCORAD; BSA, body surface area; d, days; EASI, Eczema Area and Severity Index; EASI75, improvement of greater than or equal to 75% in EASI; EASI90, improvement of greater than or equal to 90% in EASI; %EASI, percent improvement from baseline in EASI; %mEASI, percent improvement in modified EASI; FDA, Food and Drug Administration; IGA, Investigator's Global Assessment; ISGA, Investigator's Static Global Assessment; IGA0/1 or ISGA0/1, IGA 0 or 1 (clear or almost clear) plus greater than or equal to 2 grade improvement; JAK, Janus kinase; LTE, long-term extension; mo, months; mild/mod, mild-to-moderate; mild/sev, mild-to-severe; mod/sev, moderate-to-severe; NRS, numerical rating scale; OL, open-label; PDE4, phosphodiesterase 4; PGA, Physician's Global Assessment; POEM, patient-oriented eczema measure; RDBPCT, randomized, double-blind, placebo-controlled trial; RDBVCT, randomized, double-blind, vehicle-controlled trial; RTBVCT, randomized, triple-blind, vehicle-controlled; SCORAD, SCORing AD; TAC, triamcinolone; TAMA, therapeutic aryl hydrocarbon receptor–modulating agent; TMT, targeted microbiome transplant; TYK2, tyrosine kinase 2; VAS, Visual Analogue Scale.

Table 2
New and Emerging Monoclonal Antibodies

	Target	Study type	Study duration	AD severity	Age	Primary end point	Other key end points	Adverse events	Status	Trial identifier
Dupilumab	IL-4R α	Parallel phase 3, RDBPCT (SOLO 1 and 2) (MONO)	16 wk	Mod/sev	≥ 18 y	IGA0/1: met	EASI75, itch NRS, POEM: met		FDA approved for ≥ 6 y	NCT02277743 NCT02277769
		Phase 3, RDBPCT (LIBERTY AD) (MONO)			12- <18 y	IGA0/1, EASI75: met	%SCORAD, itch NRS, POEM: met	Mild injection site reactions; conjunctivitis; transient eosinophilia; fewer skin infections		NCT03054428
		Phase 3, RDBPCT (LIBERTY AD PEDS) (with TCS)	16 wk	Sev	6- <12 y	IGA0/1: met	%SCORAD, EASI75, itch NRS, POEM: met		Completed	NCT03345914
		Phase 2/3, 2-part OL study (LIBERTY AD PRESCHOOL) (with TCS)	4 wk (pK)	Sev	≥ 0.5 -6 y	Safety: met	%EASI, %SCORAD: met (6 mg/kg)	None	Recruiting	NCT03346434
			16 wk	Mod/sev		IGA0/1, EASI75	%BSA, %SCORAD, itch NRS	Pending	Recruiting	
Lebrikizumab	IL-13	Phase 2b, RDBPCT, dose-finding (MONO)	16 wk	Mod/sev	≥ 18 y	%EASI: met	IGA0/1, EASI75, EASI90, itch NRS, POEM: met	Mild injection site reactions; conjunctivitis	Completed	NCT03443024
Tralokinumab	IL-13	Phase 2b, RDBPCT, dose-finding (with TCS)	12 wk	Mod/sev	18-75 y	EASI: met, IGA0/1: not met	%SCORAD, itch NRS: met	Mild injection site reactions; conjunctivitis	Completed	NCT02347176
		Phase 3 RDBPCT (ECZTRA 1 and 2) (MONO)	16 wk		≥ 18 y	IGA, EASI75: met	%SCORAD, itch NRS: Met	Conjunctivitis	Completed	NCT03131648 NCT03160885
		Phase 3 RDBPCT (ECZTRA 3) (with TCS)	16 wk	Mod/sev	≥ 18 y	IGA0/1, EASI75: met	%SCORAD, itch NRS, EASI50, EASI90: met	Injection site reactions; conjunctivitis	Completed	NCT03363854
Nemolizumab	IL-31R α	Parallel phase 2b, multicenter, RDBPCT, dose-ranging (with TCS)	24 wks	Mod/sev	≥ 18 y	%EASI: met	Itch NRS, %SCORAD: met	Increased asthma events; high CPK	Completed	NCT03100344
GBR 830	OX40	Phase 2a, RDBPCT (MONO)	16 wk	Mod/sev	≥ 18 y	Safety, reduced epidermal thickness: met	%EASI: met	Possible increased risk of infection	Completed	NCT02683928
Etokimab	IL-33	Phase 2a, single-arm, proof of concept (MONO)	140 d	Mod/sev	18-75 y	%EASI: met	%SCORAD, 5-D itch: met	Transient neutropenia	Completed	NCT03533751
REGN 3500	IL-33	Phase 2b, dose-ranging, parallel group, RDBPCT	16 wk	Mod/sev	18-75 y	n/a	n/a	n/a	Ongoing	NCT03738423
Spesolimab	IL-36R	Phase 2a, RDBPCT (given intravenously)	16 wk	Mod/sev	18-75 y	n/a	n/a	n/a	Completed	NCT03822832

Abbreviations: BSA, body surface area; CPK, creatine phosphokinase; EASI, Eczema Area and Severity Index; %EASI, percent improvement from baseline in EASI; EASI50, improvement of greater than or equal to 50% in EASI; EASI75, improvement of greater than or equal to 75% in EASI; EASI90, improvement of greater than or equal to 90% in EASI; IGA, Investigator's Global Assessment; IGA0/1, IGA 0 or 1 (clear or almost clear) plus greater than or equal to 2 grade improvement; IL-4R α , interleukin-4 receptor alpha; IL-31R α , interleukin-31 receptor alpha; M, months; mod/sev, moderate-to-severe; MONO, monotherapy with TCS only as rescue; NRS, numerical rating scale; pK, pharmacokinetics; POEM, patient-oriented eczema measure; RDBPCT, randomized, double-blind, placebo-controlled trial; SCORAD, SCORing AD; %SCORAD, percent improvement from baseline in SCORAD; Sev, severe; TCS, topical corticosteroids.

Table 3
Emerging Oral Systemic Agents

	Target	Study type	Study duration	AD severity	Age	Primary end point	Other key end points	Adverse events	Status	Trial identifier
JAK inhibitors	JAK 1/2	Independent phase 3, multicenter, RDBVCT (BREEZE-AD1 and 2) (MONO)	16 wk	Mod/sev	≥18 y	vIGA0/1: met	EASI50, POEM: met	Headache; herpes simplex; high CPK; no VTE	Completed	NCT03334396 NCT03334422
		Phase 3 RDBPCT (BREEZE-AD5) (MONO)	16 wk	Mod/sev	≥18 y	EASI75: met (2 mg dose)	EASI90, IGA0/1, itch NRS: met	No VTE or malignancy	Completed	NCT03435081
		Phase 3, multicenter, RDBPCT (BREEZE-AD-PEDS) (with TCS)	16 wk		2–17 y	IGA0/1, pK	EASI75/90, % BSA, POEM, itch NRS	In progress	Recruiting	NCT03952559
Upadacitinib	JAK 1	Phase 2b, multicenter, RDBPCT (MONO)	16 wk	Mod/sev	18–75 y	%EASI: met	IGA0/1, EASI90, itch NRS, POEM: met	Acne; nausea; elevated CPK, LDL/HDL; no VTE or malignancy	Completed	NCT02925117
		Phase 3, RDBPCT (measure up 1) (MONO)	16 wk	Mod/sev	12–75 y	EASI75, vIGA0/1: met	Itch NRS: met	Acne; (limited available data); no VTE or malignancy	Completed	NCT03569293
		Phase 3 RDBPCT (measure up 2) (MONO)								NCT03607422
		Phase 1, OL multiple dose	2 Y safety monitoring	Sev	0.5–12 y	pK, safety	n/a	n/a	Recruiting	NCT03646604
Abrocitinib	JAK 1	Parallel phase 3, multicenter RDBPCT (JADE-MONO 1 and 2) (MONO)	12 wk	Mod/sev	≥12 y	IGA0/1, EASI75: met	POEM, itch NRS: met	Nausea, vomiting; headache; acne; transient low platelets; elevated CPK, LDL/HDL	Completed	NCT03349060 NCT03575871
Gusacitinib	JAK/SYK	Phase 1b, RDBPCT, dose escalation	28 d	Mod/sev	18–75 y	Safety: positive	Itch NRS, EASI50: met	Headache, nausea, diarrhea	Completed	NCT03139981
		Phase 2b RDBPCT	12 wk		18–75 y	n/a	n/a	n/a	Completed	NCT03531957

Abbreviations: BSA, body surface area; CPK, creatine phosphokinase; EASI, Eczema Area and Severity Index; %EASI, percent improvement from baseline in EASI; EASI50, improvement of greater than or equal to 50% in EASI; EASI75, improvement of greater than or equal to 75% in EASI; EASI90, improvement of greater than or equal to 90% in EASI; HDL, high-density lipoprotein cholesterol; IGA, Investigator's Global Assessment; IGA0/1, IGA 0 or 1 (clear or almost clear) plus greater than or equal to 2 grade improvement; JAK, Janus kinase; JAK/SYK, Janus kinase/spleen tyrosine kinase; LDL, low-density lipoprotein cholesterol; mod/sev, moderate-to-severe; n/a, not available; MONO, monotherapy with TCS only as rescue; NRS, numerical rating scale; pK, pharmacokinetics; POEM, patient-oriented eczema measure; RDBPCT, randomized, double-blind, placebo-controlled trial; SCORAD, SCORing AD; Sev, severe; TCS, topical corticosteroids; TYK2, tyrosine kinase 2; vIGA, Validated Investigator's Global Assessment; vIGA0/1, vIGA 0 or 1 (clear or almost clear) plus greater than or equal to 2 grade improvement; VTE, venous thromboembolic events.

vs 25.5%, $P > .05$).²³ Tolerability was excellent. In 2 parallel 8-week phase 3 RDBVCTs (TRuE-AD1 and -AD2), 53.8% and 51.3% of those on ruxolitinib vs 15.1% and 7.6% on vehicle achieved IGA0/1, respectively. In these 2 trials, 62.1% and 61.8% of the subjects on ruxolitinib vs 24.6% and 14.4% on the vehicle reached EASI75, respectively, and 52.2% and 50.7% on ruxolitinib vs 15.4% and 16.3% on the vehicle had a greater than or equal to 4-point reduction in the Itch Numeric Rating Scale, respectively.²⁴ Itch was reduced within 2 days. There was no evidence of significant systemic absorption and no notable stinging/burning, although acne was

described.²⁴ An open-label, pharmacokinetic study in pediatric subjects with AD is ongoing (NCT03257644).

Delgocitinib 0.5% ointment (pan-JAK inhibitor) is now approved in Japan for adults with AD, and studies are planned for other countries. In a phase 3 RDBVCT and open-label, long-term extension, subjects 16 years and older with moderate-to-severe AD reached significantly greater reductions in modified EASI score (44.3% vs 1.7%), face and neck IGA (22.8% vs 4%), and itch NRS after 4 weeks of twice daily delgocitinib 0.5% ointment vs. vehicle, respectively. Delgocitinib was generally well tolerated.²⁵ In

addition, ATI-502, a JAK1/3 inhibitor, was applied twice daily in a phase 2a open-label, 8-week study in adults with moderate-to-severe AD, leading to a physician's global assessment of 0/1 by week 4 in 41.2% of the subjects with maximum improvement in itch by week 2 and no AEs.²⁶

Therapeutic Aryl Hydrocarbon Receptor–Modulating Agent

Tapinarof, the first therapeutic aryl hydrocarbon receptor–modulating agent, improves the expression of skin barrier genes, regulates the expression of T_H2 cytokines, and protects against inflammation-associated oxidative damage.²⁷ In a 12-week, phase 2b, dosing-finding, RDBVCT, adolescents and adults with moderate-to-severe AD on 1% twice daily tapinarof vs vehicle achieved a significant difference in IGA0/1 (53% vs 24%, respectively), EASI75 (60% vs 26%), and itch NRS (30% vs 5%). AEs were largely mild, most frequently folliculitis.²⁸

Antimicrobial Agents: AMP and Topically Applied Commensal Organisms

Omiganan gel is an AMP with broad-spectrum activity against gram-positive and gram-negative bacteria and fungi.²⁹ In a 28-day, phase 2, RDBVCT in adults with mild-to-moderate AD, 2.5% omiganan led to significant improvements in SCORAD (SCORing atopic dermatitis), body surface area, morning itch, and dybiosis when compared with the vehicle. No local AEs were reported.²⁹ Given the reduction in microbial diversity with AD flares and the recognized exacerbation of AD by *S aureus*, topical supplementation with commensal organisms that kill *S aureus* has been proposed as therapy.¹³ Isolation of *S hominis* with anti-*S aureus* activity, bacterial expansion, and application to lesional skin in adults with AD (targeted microbiome transplant) reduced *S aureus* within 24 hours of application.³⁰ The targeted microbiome transplant lotion (with *S hominis* strains that optimally kill *S aureus*) had no safety issues in a phase 1/2 RDBVCT when applied twice daily in adults with moderate-to-severe AD (NCT03151148). *Roseomonas mucosa*, a gram-negative commensal bacterium that is depleted in AD, had anti-*S aureus* activity in mouse and cell culture models and reduced pruritus and SCORAD when applied twice daily to the antecubital area of 10 adults and 5 children with AD in a phase 1/2 open-label trial.³¹

Subcutaneously Administered Monoclonal Antibodies for Moderate-to-Severe AD

Dupilumab, Targeting the IL-4 Receptor

Dupilumab, the first biologic approved by the FDA for moderate-to-severe AD, binds to the IL-4R α , inhibiting IL-4 and IL-13 signaling. In the 2 pivotal 16-week parallel, phase 3, monotherapy, randomized, double-blind, placebo-controlled trials (RDBPCTs) (SOLO 1 and 2), 38% (SOLO 1), and 36% (SOLO 2) achieved the primary end point (IGA0/1) with dupilumab 300 mg every other week (after double-dose loading) significantly more than placebo (10% and 8%, respectively).³² The subjects on a dose of dupilumab 300 mg every other week achieved EASI75, EASI90 (90% reduction in EASI, generally equivalent to IGA0/1), itch NRS greater than or equal to 4, and improved quality-of-life measures vs placebo. Results from weekly vs every other week injection were not different, leading to the current indication of 300 mg every 2 weeks. A subsequent study in adults (CHRONOS) has revealed long-term (52-week) efficacy and safety.³³

In a similar phase 3, 16-week, monotherapy, RDBPCT in adolescents (LIBERTY AD), 300 mg (≥ 60 kg) or 200 mg (< 60 kg) dupilumab every other week more often than placebo achieved IGA0/1 (24.4% vs 2.4%), EASI75 (41.5% vs 8.2%), and improved pruritus (36.6% vs 4.8%),³⁴ leading to its FDA approval in adolescents in March 2019. Most recently, children 6 to less than 12 years of age

with severe AD were tested in a dose-finding phase 3, RDBPCT (LIBERTY AD PEDS) that allowed use of TCS.³⁵ Children weighing less than 30 kg responded best to 300 mg dupilumab every 4 weeks (vs 100 mg every other week), and those weighing more than or equal to 30 kg to 200 mg every other week (vs 300 mg every 4 weeks).³⁵ In May 2020, dupilumab was approved by the FDA in children 6 to 11 years of age with weight-based dosing. Pharmacokinetics, safety, and efficacy of dupilumab for infants and children 6 months to less than 6 years with AD have been described, based on an open-label trial with weight-based dosing.³⁶ A phase 3 RDBPCT (LIBERTY AD PRESCHOOL) is ongoing (NCT03346434).

AEs related to dupilumab have been limited to injection site reactions, conjunctivitis, and eosinophilia, generally mild-to-moderate, reversible, and in the minority of subjects. In general, skin infections are reduced, commensurate with improvement in AD.^{32,34,35} Although not described in trials, some patients taking dupilumab have noted exacerbated or new facial erythema, which often does not respond to topical antiinflammatory medication.³⁷ Evaluation sometimes discloses a causative contact allergy responsive to avoidance, but in other treatments for *Malassezia*-associated dermatitis (oral antifungal medication), *Demodex*, or increasing dupilumab dosing has been required to improve the facial erythema.³⁸ Psoriasiform dermatitis after initiation of dupilumab has been described and hypothesized to relate to skewing toward the T_H1/T_H17 pathway with suppression of the T_H2 pathway. Both occurrence of and improvement in alopecia areata have been noted in patients with AD on dupilumab.

IL-13 Inhibitors

Lebrikizumab binds soluble IL-13 to prevent IL-13 receptor alpha (IL-13R α) heterodimerization with IL-4R α and signaling through the IL-4 receptor. In a phase 2, dose-finding, RDBPCT, lebrikizumab 250 mg every 2 weeks was superior to placebo for IGA0/1 (44.6% vs 15.3%), EASI75 (60.6% vs 24.3%), and greater than or equal to 4-point improvement in itch NRS (70% vs 27.3%). Lebrikizumab led to slightly more injection site pain (5.3% vs 1.9%) and conjunctivitis (2.7% vs 0%) than placebo, but skin infections occurred less often.³⁹

Tralokinumab also binds IL-13 directly and prevents its binding to both the IL-13R α 1 and the decoy IL-13R α 2. In 2 parallel 16-week phase 3, monotherapy, RDBPCTs (ECZTRA1 and 2), adults receiving 300 mg tralokinumab every 2 weeks achieved IGA0/1 in 15.8% and 22.2%, respectively, vs in 7.1% and 10.9% of the controls. Significantly higher EASI75 responses (25% and 33.2% vs 12.7% and 11.4%) and pruritus NRS greater than or equal to 4 points (20% and 25% vs 10.3% and 9.5%) were noted in tralokinumab-treated patients. Rates of injection site reactions and conjunctivitis (7.1% vs 2% in ECZTRA1; 3% vs 1.5% in ECZTRA 2) were higher in patients receiving tralokinumab vs. placebo, but skin infections occurred less frequently.⁴⁰ An additional phase 3 RDBPCT with concomitant TCS (ECZTRA3) led to IGA0/1 in 38.9% of tralokinumab-treated patients vs 26.2% of those on placebo and to EASI75 in 56% on tralokinumab vs 35.7% on placebo; the AEs were similar to those in ECZTRA1 and 2.⁴¹

IL-31 Inhibitor

Nemolizumab targets the IL-31 receptor, which is thought to be key in AD itch. In 12-week, phase 2 RDBPCTs, the pruritus visual analogue scale score with nemolizumab 0.5 mg/kg every 4 weeks was reduced by 59.8% vs 20.9% with placebo by study end and was significantly less than placebo within 1 week after initiation.^{42,43} In a 24-week, phase 2b, dose-finding RDBPCT, nemolizumab 30 mg (the equivalent of the 0.5 mg/kg) every 4 weeks, together with TCS, resulted in a significantly reduced percentage in peak itch NRS (primary end point) vs placebo (67.3% vs 35.8%), sleep disturbance NRS (74.8% vs 43%), and EASI score (68.8% vs 52.1%) by week 24. The AEs included creatinine phosphokinase (CPK) elevation and

increased incidence of mild asthma events in patients with pre-existing asthma (12.3% with 30 mg nemolizumab vs 1.8% with placebo).⁴⁴

Targeting Other Cytokines and Receptors: OX40, TSLP, IL-33, IL-36, IL-5, and the Th17/IL-22 Pathway

The GBR 830, targeting OX40 in the Th2 pathway, was administered as 2 10 mg/kg intravenous doses, 4 weeks apart, in a phase 2a RDBPCT in adults. At day 71, GBR 830 met end points of significant reduction in epidermal thickness, reduction in some mRNA expression biomarkers, and greater percentage reduction in EASI score vs placebo (67.4% vs 38.2%) (NCT02683928). Although the AEs were mild, some patients given GBR 830 developed cutaneous infections at biopsy sites.⁴⁵

In a phase 2 RDBPCT that allowed TCS, tezepelumab, a TSLP inhibitor, given as 280 mg every 2 weeks, achieved numerically but not significantly greater EASI50 than placebo.⁴⁶ A dose-finding monotherapy RDBPCT is ongoing with tezepelumab (NCT03809663). Etokimab, which targets IL-33, was evaluated in a 16-week, phase 2b RDBPCT (ATLAS) but failed to achieve its primary end point of significantly higher reduction in EASI score than placebo (NCT03533751) and is no longer being tested for AD. A phase 2b RDBPCT to evaluate the safety, pharmacokinetics (pK), and efficacy of another IL-33 inhibitor, REGN 3500, is currently active (NCT03738423). Adults with AD failed to achieve a better IGA or reduction in EASI score in a phase 2 trial with mepolizumab, an anti-IL-5 antibody, compared with placebo (NCT03055195). A 16-week, phase 2a RDBPCT was recently completed, in which adults were given spesolimab, targeting the IL-36 receptor, every 4 weeks intravenously (with subcutaneous administration planned for future trials); results are pending (NCT03822832).

Although IL-22 is increased in AD and thought to play a role in epidermal hyperproliferation, a phase 2a clinical trial with fezakinumab (anti-IL-22) for adults with moderate-to-severe AD only led to significant improvements in the primary efficacy end point, SCORAD, in patients who were stratified by their severity or higher baseline levels of cutaneous IL-22 expression, suggesting for the first time a personalized approach to choosing a biologic.⁴⁷ Although fezakinumab is not advancing, ARGX112, an anti-IL-22 receptor antibody, is in phase 1 trial (NCT03514511). The Th17 pathway has also been suggested as a potential target, given its increased expression in intrinsic AD, Asians, and children with AD (in addition to their strong cutaneous T_H2 skewing). However, secukinumab (IL-17A inhibitor) monotherapy did not cause significant improvements in epidermal thickness, EASI, or SCORAD at the end of treatment compared with placebo-treated patients in a phase 2 RDBPCT, despite the majority of patients being Asian or having intrinsic AD.⁴⁸ In addition, MOR106, given intravenously to adults to target IL-17C in a 12-week, phase 2 RDBPCT, revealed early signs of failing to achieve a significant reduction in EASI score, and attempts to transition to subcutaneous administration were terminated (NCT 03568071). Other monoclonal antibodies in early trials include risankizumab (anti-IL-23p19; phase 2/ NCT03706040), bermekimab (anti-IL1-alpha; phase 2/ NCT03496974), and FB825 (anti-IgE-expressing B cells; phase 2/ NCT03758716).

Oral Small Molecule Inhibitors for Moderate-to-Severe AD

Janus Kinase Inhibitors

Oral JAK inhibitors are currently approved by the FDA for rheumatoid arthritis (tofacitinib, baricitinib, upadacitinib) and myelofibrosis and polycythemia vera (ruxolitinib). Baricitinib, abrocitinib, and upadacitinib are under investigation for patients with AD. In 2 parallel phase 3 monotherapy RDBPCTs, more patients

with moderate-to-severe AD achieved validated IGA0/1 (vIGA0/1) at 16 weeks with baricitinib, a JAK 1/2 inhibitor, than placebo (1, 2, and 4 mg in BREEZE-AD1; only 2 mg and 4 mg in BREEZE-AD2). Although the best improvements have been achieved with 4 mg dosing, the occurrence of deep vein thrombosis and pulmonary embolism at 4 mg daily dosing in the studies of rheumatoid arthritis capped the approved dosing of the FDA in the United States to 2 mg.^{49,50} In a subsequent phase 3 RDBPCT (BREEZE-AD5), adults were randomized to placebo, baricitinib 1 mg, or baricitinib 2 mg. At week 16, significantly more patients receiving baricitinib 2 mg vs placebo achieved EASI75 (29.5% vs 8.2%), EASI90 (20.5% vs 3.4%), IGA0/1 (24% vs 5.4%), and reduced itch NRS (39.9% vs 18%). No malignancies, deep vein thrombosis, or pulmonary embolism were observed.^{51,52} Mild, self-resolving headaches, asymptomatic increases in CPK, and in BREEZE-AD1, herpes simplex infections (5.3% with baricitinib vs 1.2% with placebo) have been reported.

Upadacitinib, a JAK 1 inhibitor, had optimal efficacy in a phase 2b monotherapy RDBPCT in adults with moderate-to-severe AD with 30 mg daily dosing.⁵³ In phase 3 RDBPCTs (Measure Up 1 and 2), 80% and 73% of adolescents/adults achieved EASI75 with 30 mg daily dosing (vs 16% and 13% for placebo) and significant improvement vs placebo in vIGA (62% and 52% vs 8% and 5%) and peak itch NRS greater than or equal to 4 (60% in both vs 12% and 9%) by treatment end at 16 weeks. New-onset acne was noted more often with upadacitinib 30 mg (17.2% and 14.5%) vs placebo (2.1% and 2.2%), but not eczema herpeticum. No malignancies or emboli were described.⁵⁴ In the phase 2 trial, more patients receiving upadacitinib had nausea, acne, headaches, and mild-to-moderate CPK and lipid elevations.⁵³

Notably, 2 parallel phase 3 RDBPCTs with abrocitinib (JAK 1 antagonist) for adolescents and adults with moderate-to-severe AD (JADE-MONO 1 and 2) were recently completed. In MONO 2, abrocitinib 200 mg daily had greater improvements than placebo in IGA (38.1% vs 9.1%), EASI75 (61% vs. 10.4%), and itch NRS greater than or equal to 4 (55.3% vs 11.5%).⁵⁵ The AEs included mild elevations in CPK and lipids, transient thrombocytopenia, nausea, acne, and headaches. Results were similar in the JADE-MONO 1 study.

An early phase 1b RDBPCT suggested the safety and efficacy of 80 mg daily gusacitinib, a JAK/spleen tyrosine kinase (JAK/SYK) inhibitor.⁵⁶ A phase 2b study to further evaluate the efficacy of gusacitinib was recently completed (NCT03531957), but data are unavailable.

Other Small Molecule Inhibitors

Given the importance of pruritus in disease pathogenesis and AD impact, potential therapies that directly target the neuro-immune axis and reduce the cutaneous sensation of itch are of great interest (Fig 2). However, beyond nemolizumab targeting the IL-31 receptor (Monoclonal Antibodies), other agents with neuron-based targets have been disappointing or are in early trials. ZPL-3803787, a histamine 4 receptor (H4R) antagonist, failed to achieve its primary and secondary efficacy end points in a phase 2b RDBPCT in adults with moderate-to-severe AD.⁵⁷ Serlopitant, an antagonist of the NK-1 receptor, which typically binds substance P, did not meet primary itch or secondary end points in a phase 2 RDBPCT (NCT01951274), despite its better efficacy for chronic pruritus and prurigo nodularis.⁵⁸ Asimadolin, a selective oral kappa opioid receptor agonist, met the primary (safety) and secondary (improved nighttime itch and quality of life) end points in a recent phase 2 clinical trial (NCT02475447). Finally, PAC-14028, a TRP cation channel subfamily V member 1 antagonist, met primary (reduced lesional severity) and secondary (pruritus) end points in a phase 2b clinical trial (NCT02757729).^{59,60} New small molecule inhibitors in early trials are etrasimod (selective sphingosine 1-

phosphate receptor antagonist; phase 2/NCT04162769) and RPT193 (chemokine receptor 4 inhibitor; phase 1/NCT04271514).

Conclusion

Our expanding knowledge of the complex pathomechanisms of AD has given rise to new targeted therapeutic interventions. The FDA has approved the topical PDE4 inhibitor, crisaborole 2% ointment, for mild-to-moderate disease as young as 3 months of age and a monoclonal antibody, dupilumab, for moderate-to-severe disease as young as 6 years of age. Phase 2 and 3 clinical trials with emerging topical and systemic targeted drugs have promising results with respect to efficacy and safety profiles. Future trials will address the long-term safety and durability of these new medications and ideally define subpopulations who are best suited for the many upcoming therapeutic options.

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