

Therapeutic pipeline for atopic dermatitis: End of the drought?



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List of Design Committee Members: Amy S. Paller, MS, MD, Kenji Kabashima, MD, PhD, and Thomas Bieber, MD, PhD, MDRA (authors); Stephan Weidinger, MD, PhD (editor)

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: A. S. Paller has consultant arrangements with Dermira, Eli Lilly, Galderma, GlaxoSmithKline-Stiefel, Novartis,

Pfizer, Regeneron/Sanofi, Roivant, and Valeant and has received grants from AbbVie, Celgene, LEO, and Novartis. K. Kabashima has consultant arrangements with Chugai and Maruho and has received grants from Japan Tobacco. T. Bieber has consultant arrangements with Astellas, Sanofi/Regeneron, Pfizer, Novartis, Lilly, Galderma, Roivant, Menlo TX, GlaxoSmithKline, and Daiichi-Sankyo; has received payment for lectures including Astellas, Pfizer and Sanofi; and has received payment for manuscript preparation from Sanofi/Regeneron. S. Weidinger disclosed no relevant financial relationships.

Activity Objectives:

1. To be able to name several targets of pharmacologic and biologic drugs in development for atopic dermatitis (AD) in the pathways of inflammation.
2. To know the mechanism of action of recently approved pharmacologic and biologic drugs for AD.
3. To describe the main differences in the cutaneous microbiome between AD skin and normal skin.

Recognition of Commercial Support: This CME activity has not received external commercial support.

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The exam authors disclosed no relevant financial relationships.

Until the past year, our therapeutic armamentarium for treating atopic dermatitis (AD) was still primarily topical corticosteroids and, for more severe disease, systemic immunosuppressants. The pipeline of more targeted topical and systemic therapies is expanding based on our growing understanding of the mechanism for AD and is particularly focused on suppressing the skewed immune activation. Most agents are in phase 2 clinical trials. Crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, became available in late 2016 in the United States for mild-to-moderate AD, with other PDE4 inhibitors, an agonist of the aryl hydrocarbon receptor, Janus kinase inhibitors, and commensal organisms also in trials for topical application. The first highly effective mAb for

AD, dupilumab, targets the IL-4/IL-13 receptor and was approved in early 2017 in the United States for moderate-to-severe adult AD. Other biologics similarly inhibit T_H2 cytokines (thymic stromal lymphopoietin, IL-4, IL-5, IL-13, and the itch-specific cytokine IL-31 and their receptors) or T_H22/T_H17 cytokines, levels of which are increased in lesional skin. Orally administered small-molecule inhibitors that suppress inflammation (targeting chemoattractant receptor-homologous molecules expressed on T_H2 lymphocytes, PDE4, the histamine 4 receptor, and Janus kinase) or specifically itching (eg, NK1R inhibitors) are also being studied. Comparing biomarkers with individual responses to experimental agents will help to determine subphenotypes

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2017.07.006>

within AD that predict prognosis and treatment responses. (*J Allergy Clin Immunol* 2017;140:633-43.)

Key words: *Biologics, small molecule inhibitors, topical therapy, cytokines, mAbs, precision medicine*

Atopic dermatitis (AD; also known as atopic eczema) is one of the most common inflammatory skin disorders worldwide, with an increasing incidence during the past few decades, especially in developed countries. The point prevalence estimates in the United States are 11% to 13% for children^{1,2} and 7% for adults.³ AD is of at least moderate severity in 33% of affected children,⁴ with the percentage increasing with advancing age.² Itch/pruritus is a hallmark of AD, and the associated discomfort of the disease and high visibility lead to sleep deprivation and adverse psychosocial effects.

A growing number of comorbidities are recognized to be associated with AD.⁵ The propensity toward allergic disorders (food allergy, asthma, allergic rhinoconjunctivitis, and eosinophilic esophagitis) and skin infection (especially *Staphylococcus aureus* and widespread herpes/eczema herpeticum) is clearly increased, but neuropsychiatric issues (attention deficit hyperactivity disorder, depression, anxiety, conduct disorder, autism, and suicidal ideation)⁶⁻¹⁰ have been linked more recently. Although earlier evidence suggested a link with cardiovascular disease,^{11,12} more recent primary studies and meta-analyses have provided evidence against an association with AD.¹³⁻¹⁶ Although the link with malignancy is also controversial, there is some evidence of an association of severe AD with lymphoma in cohort (but not case-control) studies,¹⁷ possibly related to the chronicity of the inflammatory disease.

In addition, the economic burden is high, with the average annual cost conservatively estimated to be \$5.3 billion in the United States¹⁸; out-of-pocket expenses can be as high as 10% of the household annual income.¹⁹ Indirect costs are difficult to measure but include missed school or work and expenses associated with medical visits. These economic costs do not take into account the additional burden of comorbidities, which add another 150% in costs for associated allergic disorders alone.²⁰ The high prevalence, chronicity, costs for health care, and risk of comorbidities exert a profound negative effect on the quality of life of affected subjects, as well as their families.¹⁸

THE NEED FOR NEW THERAPEUTICS FOR AD

The mainstay of treatment for AD for decades has been topical corticosteroids. For more severely affected subjects, systemically administered broad immunosuppressant drugs (cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and short courses of systemic corticosteroids) are used.²¹ Topical steroid use has been associated with largely cutaneous adverse events, most often skin thinning (atrophy and striae). Systemic agents all have several drug-specific risks and broadly suppress the immune system. Until this past year, the only new class of medications for treating AD contained the topical calcineurin inhibitors tacrolimus and pimecrolimus, which have been commercially available since 2000 and 2001, respectively. Although without the potential risks of topical steroids, topical calcineurin inhibitors have often been associated with burning/stinging and have had a black box warning associated with their use based on the early theoretic risk of increased nonmelanoma skin cancer and lymphoma.

Abbreviations used

AD:	Atopic dermatitis
AhR:	Aryl hydrocarbon receptor
CRTH2:	Chemoattractant receptor homologous molecules expressed on T _H 2 lymphocytes
EASI:	Eczema Area and Severity Index
FLG:	Filaggrin
GRPR:	Gastrin-releasing peptide receptor
H4R:	Histamine receptor type 4
JAK:	Janus kinase
PDE4:	Phosphodiesterase 4
PoC:	Proof of concept
STAT:	Signal transducer and activator of transcription
TSLP:	Thymic stromal lymphopoietin

During the past decade, the underlying molecular basis for AD has been increasingly understood, particularly with a focus on barrier dysfunction, cutaneous and systemic immune abnormalities, and the role of the microbiome, allowing development of more targeted therapies.²² Although debate has focused on whether AD pathogenesis is primarily “inside-out” (primary role of the immune system) versus “outside-in” (primary role of the epidermal barrier), it is now clear that the barrier, immune system, and microbes are all interconnected, with each abnormality progressively exacerbating another until successful intervention is introduced. In addition, the underlying basis for itch at the peripheral and central nervous system levels is an active area of investigation.²³ Importantly, our increased understanding of these factors that contribute to AD has enabled the development of new therapies targeted toward suppressing activated immune pathways, improving the epidermal barrier, normalizing the skewed microbial populations on affected skin, and reducing the itch. These emerging medications for AD can take the form of topical products (Table I), mAbs (Table II) or small-molecule inhibitors (Table III).

THE EFFECT OF CUTANEOUS IMMUNE RESPONSES ON THE SKIN BARRIER

The skin provides a barrier that protects from the external environment. This barrier is comprised of epidermal proteins of the stratum corneum, stratum granulosum, and tight junctions, as well as epidermal lipids, such as ceramides. When this barrier is impaired, external stimuli (eg, irritants, bacteria, and dust mite and food protein allergic triggers) can more easily induce inflammation.

During the past decade, several studies have demonstrated that skin barrier dysfunction is a critical component of AD.²⁴ Having high transepidermal water loss, a measure of barrier dysfunction, at 2 days of age is associated with a 7.1-fold higher increased risk of having AD by 1 year of age than having low transepidermal water loss.²⁵ In addition, having an inherited deficiency in epidermal barrier proteins (notably filaggrin [FLG]) increases the risk of AD and allergic disorders, presumably by attenuating the skin barrier, facilitating the interaction of external antigens with skin-resident immune cells and driving the cutaneous inflammation that leads to systemic immune responses.²⁴ These observations suggest that maintaining skin barrier function is important for the effective management of AD. However, even

TABLE I. New or in the pipeline: Topicals

Target	Compound	Indication	Phase
AhR	Tapinarof/benvitimod	Moderate-severe	2a →
PDE4	Crisaborole (Eucrisa)	Mild-moderate	3 in EU (FDA 2016)
PDE4	Roflumilast	Moderate	2a → ?
PDE4	RVT-501	Mild-moderate	2a →
JAK1, JAK3	Tofacitinib	Moderate-severe	2a → STOP
JAK1, JAK2	INCB18424	Mild-moderate	2a →
JAK1, JAK3	LEO 124249/JTE-052	Mild-moderate	2a
<i>S aureus</i>	R mucosa bacteria	Antecubital AD	1/2
<i>S aureus</i>	Coagulase-negative <i>Staphylococcus</i>	Moderate-severe on ventral arms	1/2

→, Drug development program is ongoing, phase 3 is planned but not yet running; →?, unknown future of drug development program; → STOP, drug development program has been stopped; EU, European Union; FDA, US Food and Drug Administration.

TABLE II. New or in the pipeline: Biologics

Target	Compound	Indication	Phase
TSLP	Tezepelumab	Moderate-severe	2a →
Ora1	Anti-Ora1	Moderate-severe	2a →
IL-4/IL-13R	Dupilumab (Dupixent)	Moderate-severe	Approved by FDA, 2017; approval pending in EU
IL-4	Pitrakinra	Moderate-severe	2a → ?
IL-13	Tralokinumab	Moderate-severe	3
IL-13	Lebrikizumab	Moderate-severe	3
IL-5	Mepolizumab	Moderate-severe	2a
IgE	QGE031/ligelizumab	Moderate-severe	2a → ?
IL-12/IL-23	Ustekinumab (Stelara)	Moderate-severe	2a →
IL-22	Fezakinumab (intravenous)	Moderate-severe	2a →
IL-17A	Secukinumab (Cosentyx)	Moderate-severe	2a →
IL-31 receptor A	CIM331/nemolizumab	Moderate-severe	2b →
IL-31	BMS-981164	Moderate-severe	1b → ?

→, Drug development program is ongoing, phase 3 is planned but not yet running; →?, unknown future of drug development program; EU, European Union; FDA, US Food and Drug Administration.

without *FLG* mutation, *FLG* expression in adults with AD is decreased, implicating factors associated with disease chronicity.

It has been demonstrated that T_H2 cytokines (IL-4 and IL-13) downregulate the production of (1) FLG and keratins,²⁶ (2) cornified envelope components (loricrin and involucrin), (3) cell adhesion molecules (desmogleins and zonula occludens 1), and (4) ceramide lipids. IL-31, another T_H2 cell-derived cytokine and known as a pruritogen, also downregulates FLG expression.²⁷ A recent study has shown that IL-33, an alarmin that is abundantly produced in the epidermis of patients with AD, has the potency to downregulate *FLG* expression as well.²⁸

TACKLING THE “T2 CONNECTION” IN PATIENTS WITH AD

Since the discovery of IL-4 and its role in regulating IgE synthesis in the 1980s, an increasing stratification in the spectrum of the helper T-cell response has been established, leading to the concept of T_H1 , T_H2 , T_H9 , T_H17 , and T_H22 cells. This concept has been widened to include innate lymphoid cells with similar cytokine profiles. Nowadays, in addition to other immunologic pathways,²⁹ the so-called T_H2 immune pathway³⁰ has been recognized as an important mechanism involved not only in driving IgE synthesis but also in many inflammatory reactions. Overall, this pathway can be considered to start in the skin as the site of sensitization and ultimately leads to the inflammatory reaction. It can be schematically summarized, as shown in Fig 1, which also depicts the different possible targets for drugs currently in development.

Agonist of the aryl hydrocarbon receptor

Increased interest has been focused on the possible role of the aryl hydrocarbon receptor (AhR) in skin physiology and control of inflammation.³¹ In the skin AhR is a ubiquitously expressed ligand-activated transcription factor, acting as a receptor for xenobiotics. Interestingly, contradictory results have been reported about the proinflammatory or anti-inflammatory outcome of AhR signaling, probably related to activation of canonical versus noncanonical pathways. In mice activation of AhR leads to (1) expression of artemin, (2) increased epidermal innervation, and (3) inflammation. In human AD skin AhR expression is increased,³² but its increased expression and activation by coal tar restores FLG expression in FLG-haploinsufficient keratinocytes and interferes with the T_H2 cytokine signaling.³³ The latter report strongly implies that AhR is not only a target for topical anti-inflammatory therapy, but also for restoration of epidermal barrier function. Indeed, a new class of therapeutic compounds has been defined, and its first representative is the AhR agonist tapinarof (GSK2894512; formerly, WBI-1001; in China, benvitimod). WBI-1001 showed encouraging results in early trials,^{34,35} and a pharmacokinetic trial of tapinarof in adult AD (NCT02466152) and a dose-finding trial in adolescents and adults with AD (NCT02564055) were recently completed.

Thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is known as a keratinocyte-derived cytokine that leads to conditioning of skin-derived dendritic cells, ultimately generating a strong T_H2

TABLE III. New or in the pipeline: Small molecules

Target	Compound	Indication	Phase
CRTH2	OC000459	Moderate-severe	2a → STOP
CRTH2	QAW 039	Moderate-severe	2b → STOP
PDE4	Apremilast (Otezla)	Moderate-severe	2a → STOP
H4R	ZPL389	Moderate-severe	2a →
JAK 1/2	Baricitinib	Moderate-severe	2b →
JAK 1	Pf-04965842	Moderate-severe	2a →
JAK 1	Upadacitinib (ABT 494)	Moderate-severe	2a →
NK1R	VLY-686/tradipitant	Moderate-severe	2a →
NK1R	Serlopitant	Moderate-severe	2a →

→, Drug development program is ongoing, phase 3 is planned but not yet running;
→ STOP, drug development program has been stopped.

response.³⁶ Thereby TSLP seems to deliver important signals for the overall sensitization mechanisms initiated on contact of allergens in inflamed skin.³⁷ Moreover, in animal models TSLP has been reported to be key in the mechanisms underlying the atopic march.³⁸ TSLP, which is regulated in keratinocytes by the ORAI1/NFAT calcium-signaling pathway, also directly communicates with a subset of transient receptor potential A1⁺ sensor cutaneous sensory neurons to promote pruritus.³⁹ Currently, tezepelumab, an anti-TSLP antibody, has completed phase 1 (AMG 157; NCT00757042) and phase 2a (MEDI9929; NCT02525094) trials in patients with AD, respectively. Theoretically, tezepelumab has the potential to affect sensitization pathways rather than control of the cutaneous inflammatory reaction itself. Recently, a promising fusion protein targeting receptors for both TSLP and IL-7 (IL-7RA) has been described.⁴⁰

Chemoattractant receptor-homologous molecules expressed on T_H2 lymphocytes

In the quest for T_H2-specific markers, a prostaglandin D₂ (PGD₂) receptor (chemoattractant receptor-homologous molecules expressed on T_H2 lymphocytes [CRTH2]) was found to be expressed on inflammatory T_H2 cells,⁴¹ type II innate lymphoid cells, eosinophils, and basophils. Mast cells have been speculated to be a potential source of PGD₂ in AD skin, which would act on CRTH2 and initiate migration of T_H2 cells into the skin. A series of proof-of-concept (PoC) studies have been initiated with 2 different representatives of a new class of compounds (OC000459 and fexipriant/QAW039); posted results from QAW039 suggest lack of significant efficacy (NCT01785602). Ongoing studies are testing effectiveness for disorders with a more prominent role for eosinophils (eosinophilic esophagitis and eosinophilic asthma).

IL-4 and IL-13

IL-4 and IL-13 are the 2 most important cytokines involved in regulation of IgE synthesis, as well as in generating "atopic inflammation." Recent evidence has also suggested that the shared receptor subunit for IL-4 and IL-13 (IL-4Ra) on sensory neurons can mediate chronic pruritus through Janus kinase (JAK) signaling.⁴² Dupilumab, a biologic targeting IL-4Ra, has recently been approved in the United States for therapy of moderate-to-severe forms of AD. In the pivotal set of phase 3 studies, dupilumab led to an improvement of at least 75% from baseline to week 16 in the Eczema Area and Severity Index (EASI) score

in 13% of subjects receiving placebo but 48% on every other week dupilumab and 50% on every week dupilumab ($P < .001$ for both active arms).⁴³ The approval procedure at the European Medicines Agency is expected to be completed by the end of 2017 in the European Union. A study of dupilumab in adolescents with moderate-to-severe AD has recently been completed in Europe, and one has just started in the United States. Because this review is dedicated to products in the pipeline and the clinical efficacy and safety of dupilumab in adults has been extensively reported, this new drug will not be discussed further.

Another strategy is to block specifically either IL-4 or IL-13. PoC trials for AD have been completed for pitrakinra, an antagonist of IL-4 (NCT00676884, no results available to date), and tralokinumab and lebrikizumab, both biologics targeting IL-13 (NCT02347176, NCT02340234, and NCT02465606). Although no significant improvement was described in unpublished reports of the latter, the use of topical steroids in these trials might have obscured the difference between the placebo and active treatment arms. A study testing tralokinumab as monotherapy is planned (NCT03131648) to further test the efficacy of the anti-IL-13 strategy.

IL-5

Among T2 cytokines, IL-5 attracts eosinophils within the inflamed tissue and thus represents an ideal target to inhibit the migration of eosinophils, which plays a key role in subsets of patients with asthma and eosinophilic esophagitis, although their role in AD is unclear. Mepolizumab is an anti-IL-5 biologic, which has been approved recently in the United States and European Union for severe eosinophilic asthma. This compound did not fulfill expectations in a short-term pilot study in patients with AD,⁴⁴ but given the improvement for eosinophilic asthma, it is possible that stratification of patients with AD based on the presence of eosinophilia would select potentially responsive patients. New studies have been initiated to address the long-term risk/benefit ratio of mepolizumab in a subset of patients with AD with increased eosinophil counts (NCT03055195).

Phosphodiesterase 4

The intracellular cyclic AMP level is regulated by phosphodiesterase 4 (PDE4) activity and in turn modulates the generation of either proinflammatory (high level of PDE4) or anti-inflammatory (low level of PDE4) cytokines by immune cells. Increased PDE4 levels have been reported in cells from atopic subjects, and targeting PDE4 by specific inhibitors is thought to reduce the secretion of proinflammatory mediators in patients with AD.⁴⁵ The topical boron-based PDE4 inhibitor crisaborole has been approved recently by the US Food and Drug Administration in the United States for patients with mild-to-moderate AD aged 2 years and greater.⁴⁶ In the pivotal set of phase 3 studies, crisaborole-treated children and adults achieved the primary end point (clear/almost clear with ≥ 2 -grade improvement) more often than vehicle-treated patients with AD (32.8% vs 25.4% [$P = .038$] in one study and 31.4% vs 18.0% [$P < .001$] in the other).⁴⁶ Other PDE4 inhibitors are in trials. Although the systemic PDE4 inhibitor apremilast has been approved for the treatment of psoriasis and a pilot study with this compound in AD showed promising results, a double-blind, placebo-controlled PoC trial (NCT02087943) did not meet its primary end point.⁴⁷

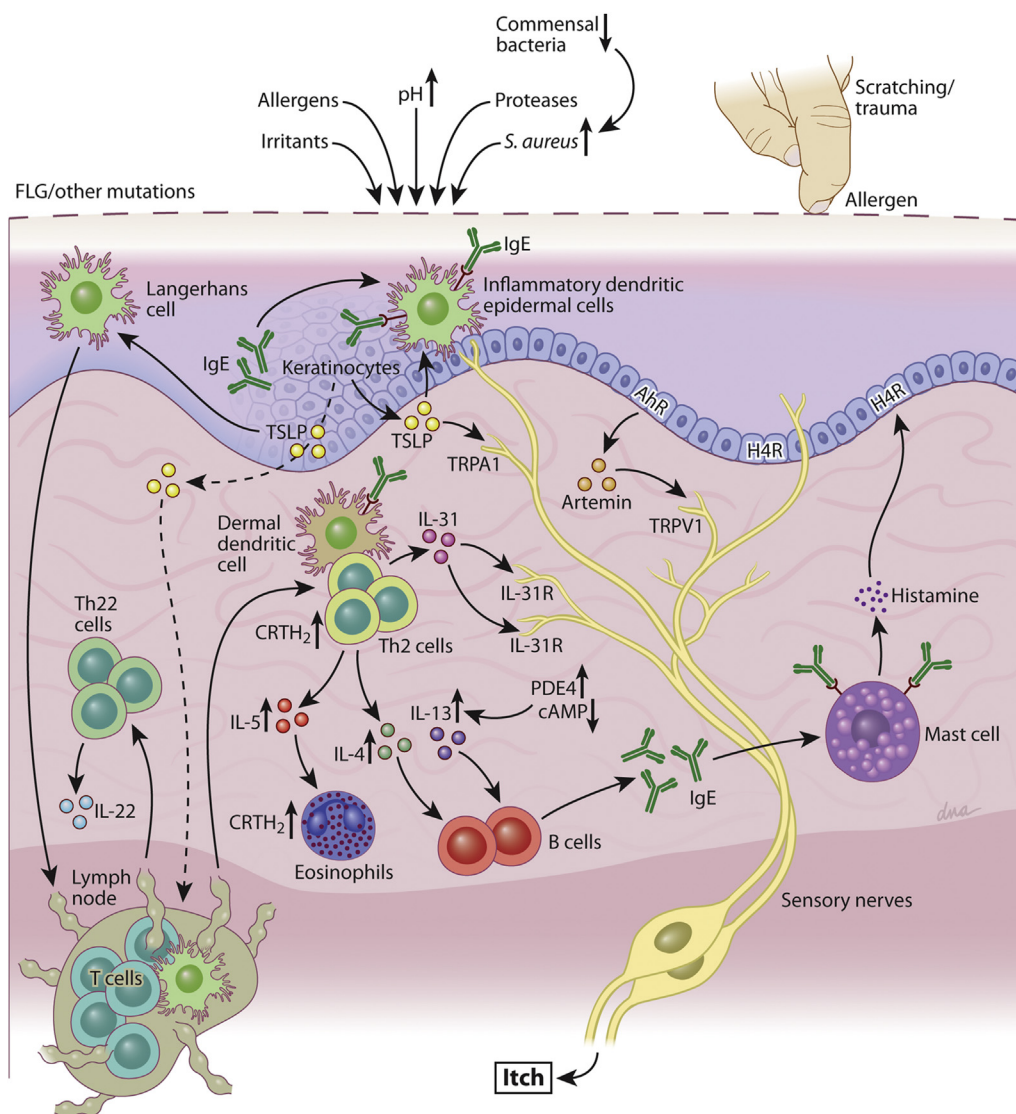


FIG 1. Interplay of the epidermis and immune system in patients with AD demonstrates the targets for new therapy. Barrier defects promote the ingress of epicutaneous antigens that interface with epidermal Langerhans cells and dermal dendritic cells, leading to immune activation, particularly of the T_H2 and T_H22 signaling pathways. CRTH2, a prostaglandin D_2 receptor on a variety of inflammatory cells, promotes T_H2 cell migration into the skin. T_H2 cytokines (ie, IL-4, IL-3, and IL-5) lead to IgE class-switching and induce peripheral eosinophils and mast cells. Increases in PDE4 also increase T_H2 cytokine expression. T_H22 cells produce IL-33, which induces epidermal hyperplasia and is prominent in patients with chronic disease. T_H2 and T_H22 cytokines also contribute to the impaired expression of barrier proteins and barrier impairment, which is thought to increase the risk of infection. *S aureus* is increased and bacterial diversity is decreased with flares. The T_H2 cytokine IL-31 is upregulated and associated with causing itch but not inflammation. TSLP production by keratinocytes not only induces a T_H2 response but is also thought to induce itch by directly stimulating transient receptor potential A1 (TRPA1) receptors in cutaneous sensory neurons. Newer targets are AhR and H4R, which is expressed on both keratinocytes and T_H2 cells and regulates IL-31 expression.

IgE

IgE is considered a hallmark of atopic diseases, including AD. Patients with AD with “normal total IgE levels” are known to have relevant amounts of allergen-specific IgE (oligo-sensitized), as determined by using RAST or chip technology. However, the anti-IgE biologic omalizumab did not show efficacy in PoC studies in adults.⁴⁸ This lack of effect does not seem to be related to affinity issues of omalizumab because the high-affinity anti-IgE compound ligelizumab

similarly did not show clinical efficacy.⁴⁹ However, a limited number of studies with omalizumab in combination with other therapies, such as the anti-CD20 biologic rituximab or intravenous immunoglobulin, suggest that a subgroup of patients might benefit from this strategy.⁵⁰ Whether the anti-IgE strategy might be more promising in a yet-to-be-defined subset of AD or in the pediatric population is currently being explored in an ongoing study in children with severe AD (NCT02300701).

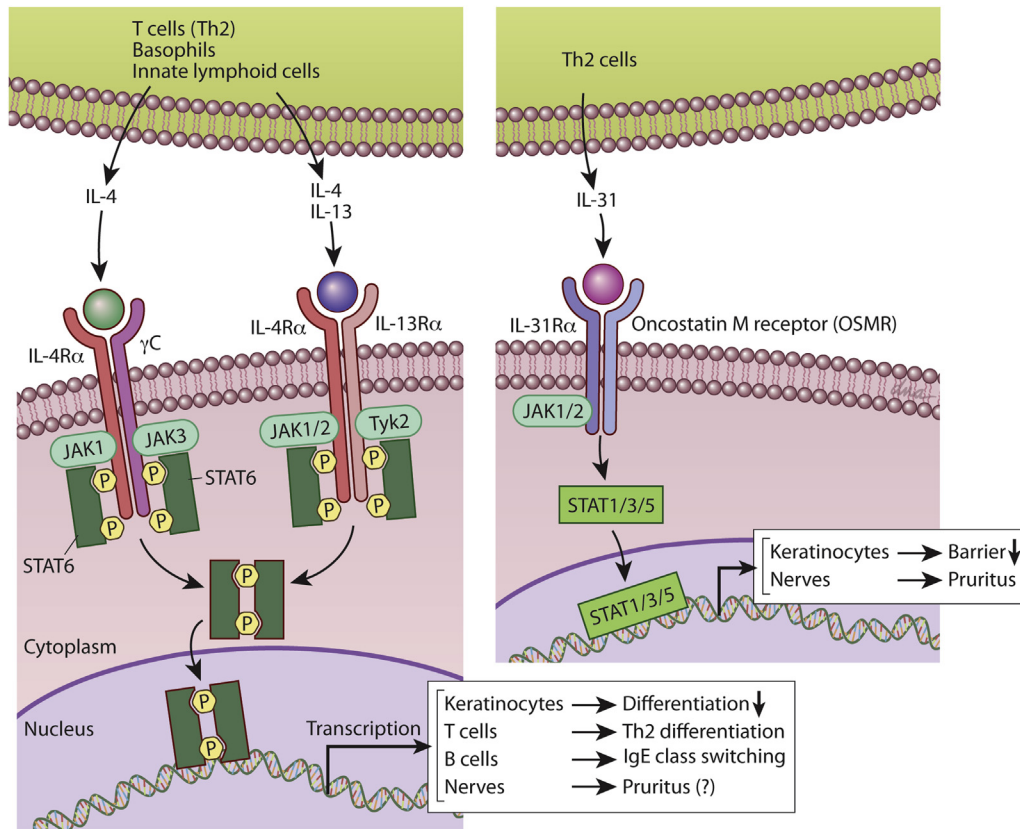


FIG 2. JAK-STAT signaling. Schematic diagram of the IL-4/IL-13/STAT6 signaling pathways through IL-4 receptor α and JAK1. γ C activates JAK3, whereas IL-13 receptor α 1 activates tyrosine kinase 2 (TYK2) and JAK2. Activated JAKs then phosphorylate STAT6. Phosphorylated STAT6 dimerizes, migrates to the nucleus, and binds to the promoters of the IL-4- and IL-13-responsive genes, such as those associated with impaired keratinocyte differentiation, T_H2 cell differentiation, IgE class-switching, and possible pruritus. Similarly, IL-31 binds to IL-31 receptor α , activates JAK1/2, and then phosphorylates STAT1/3/5. These signals lead to impaired skin barrier function and pruritus.

Histamine receptor type 4

The role of histamine as an itching-inducing mediator is well known, but the effect of medications that target classical anti-H1 and anti-H2 receptors in managing itch in patients with AD has always been disappointing.⁵¹ On the other hand, histamine levels are increased in patients with AD and assumed to be involved in the generation of inflammatory reactions. The histamine receptor type 4 (H4R) is expressed on keratinocytes and T_H2 cells, and H4 stimulation leads to IL-31 production in human subjects. In addition, the H4R antagonist JNJ777120 attenuated scratching behavior and improved dermatitis in mice,⁵² making H4R a potential target for pharmacologic intervention. Oral administration of an H4R antagonist (JNJ-39758979) to patients with AD significantly reduced pruritus but was terminated because of agranulocytosis in 2 of 27 patients with JNJ-39758979 (300 mg/d).⁵³ ZPL-389, a H4R antagonist, has completed phase 2 clinical trials for AD with promising results⁵⁴; although significant improvement in the EASI score was achieved, the primary end point of reduced pruritus was not, perhaps in part because of the concomitant use of topical steroids in both trial arms. Nevertheless, this result raises the question of whether this compound exerts primarily an anti-inflammatory rather than antipruritic effect on AD.

INHIBITING THE ACTIVATION OF OTHER HELPER T-CELL PATHWAYS

In addition to T_H2 polarization in patients with AD, increases in lesional skin of T_H1 , T_H17 , and particularly T_H22 cytokine levels have also been described.⁵⁵ Several case reports and case series have suggested the efficacy of the IL-12/IL-23p40 antibody ustekinumab, which regulates T_H1 and T_H17 pathways, in improving the severity of AD.⁵⁶ Nevertheless, 2 recent double-blind, randomized trials, one in 79 Japanese patients with AD (NCT01945086) and the other in 33 US patients (NCT01806662),⁵⁷ did not demonstrate significant improvement.⁵⁸ However, these studies might have been underpowered (there was a trend toward efficacy), and topical corticosteroid use was allowed in both. A recent double-blind, randomized trial with 60 patients of an anti-IL-22 (fezakinumab) mAb (NCT01941537) showed significant improvement only in the severely affected patients with AD.⁵⁹ Given the variable responses to ustekinumab and anti-IL-22 antibody, it is likely that a subset of patients with AD with more polarization toward T_H22 cytokine pathways might be responsive to ustekinumab and fezakinumab. In addition, T_H17 increases (which can contribute to increases in IL-22) have been described in some adults with AD, particularly in Asian patients,⁶⁰ and in affected children with recent-onset disease who are 5 years of

TABLE IV. Major mediators of pruritus and their receptors on C-fibers

Source	Mediator	Receptors on C-fibers
Mast cells	Histamine	HR1, HR4
	Kallikreins, tryptase, trypsin, cathepsins, and other endogenous/exogenous proteases	PAR-2
Nerves	Substance P	NK1R
Eosinophils	Reactive oxygen	TRPA1, etc
Fibroblasts	Artemin	GFR α 3
Keratinocytes	Nerve growth factor	Nerve growth factor receptor (TrkA and p75NTR)
	Semaphorin 3A	Neuropilin-1 (NRP1)
	TSLP	TSLP receptor
	IL-31	IL-31 receptor
Endothelial cells	Endothelin (ET1, ET2)	ETA, ETB
	Acetylcholine	Ach receptor

GFR, Glial cell line–derived neurotrophic factor/GDNF family receptor; HR, histamine receptor; NTR, neurotrophin receptor; PAR-2, protease-activated receptor 2; TRPA1, transient receptor potential A1.

age and less,⁶¹ although T_H2 cytokine level increases still predominate. In addition, TSLP has been shown to induce IL-17A through a CXCR2-dependent mechanism, and anti-IL-17A mAb suppressed AD-like skin lesions in mice.⁶² As a result, the T_H17 inhibitor secukinumab is also currently being studied in adults with AD (NCT02594098).

JAK INHIBITORS

JAK–signal transducer and activator of transcription (STAT) is an intracellular signaling pathway on which many different proinflammatory cytokines (eg, IL-4, IL-5, IL-13, and IL-31) elicit their pathophysiologic functions (Fig 2).⁶³ In a mouse model of AD, the topical JAK inhibitor JTE-052 decreased IL-4 and IL-13 signaling and improved skin barrier function.⁶⁴ In a phase 2a trial the mean percentage change from baseline at week 4 in EASI score was significantly greater ($P < .001$) for topical tofacitinib (81.7%) than for vehicle (29.9%).⁶⁵ Significant improvement in EASI scores was observed by week 1 and pruritus by day 2; the reduction in pruritus can result from inhibition of IL-31 signaling, which is also mediated by the JAK-STAT pathway. The capacity to restore the skin barrier in an AD mouse model could also result from suppression of IL-4/IL-13 and IL-31 signaling.^{26,27,66} Other topical JAK inhibitors, INCB18424 (JAK1/2 inhibitor; NCT03011892) and LEO 124249/JTE-052 (Pan-JAK inhibitor; in trials in Japan), are in phase 2 clinical trials. Although oral tofacitinib is commercially available and a promising systemic agent, its potential adverse events caused by immunosuppression necessitate careful long-term study if considered for AD. Several other oral JAK inhibitors are currently being evaluated: baricitinib (JAK1/2 inhibitor; phase 2 completed; NCT02576938), PF-04965842 (JAK1 inhibitor; in phase 2; NCT02780167), and upadacitinib (JAK1 inhibitor; in phase 2; NCT02925117). These trials will help define the efficacy of JAK inhibitors in patients with AD.

FOCUSING ON THE ITCH OF AD Mechanism of pruritus (mediators, hyperinnervation, and chronicity)

AD is characterized by chronic pruritus/itch that induces scratch behavior.⁶⁶ Scratch can serve as a physiologic self-protective mechanism to prevent the body from being hurt by harmful external agents²⁴ but is well recognized to damage skin and increase inflammation, which further exacerbates pruritus, leading to the “itch-scratch cycle.”

Pruritus is known to be induced by a variety of mediators (Table IV). Pruriceptive primary sensory nerves (C-fibers) transmit the pruritic signal induced by histamine-dependent and independent pruritogens (eg, proteases, house dust mite proteases, endothelin-1, IL-4, IL-13, IL-31, and chloroquine) through afferent fibers from the epidermis or dermis to the spinal cord.⁶⁶ Histamine released by immune cells activates 2 major histamine receptors: H1R and H4R. For histamine-independent pruritus, Mas-related G protein–coupled receptors and gastrin-releasing peptide receptor (GRPR) mediate the pruritic sensation in the C-fiber and dorsal spinal cord, respectively.^{67,68} Receptor activation of pruritogens on peripheral nerve endings induces electrical firing, Ca²⁺ influx, and activation of intracellular cell signaling pathways (Fig 3).

Sprouting and thickening of epidermal nerve fibers are found in human and animal AD,⁶⁹ which might explain the characteristic skin pruritus (alloknesis) produced by innocuous mechanical stimulation. Such hyperinnervation is probably caused by an imbalance of nerve elongation factors, such as nerve growth factor and IL-31, and nerve repulsion factors, such as semaphorin 3A. Topically applied semaphorin 3A ointment inhibits scratching behavior and improves skin inflammation in NC/Nga mice as a model of AD.⁷⁰

Artemin, which is secreted by dermal fibroblasts in response to substance P, has also received attention recently. Artemin leads to abnormal peripheral innervation and thermal hyperalgesia,⁷¹ probably by decreasing the threshold of the temperature-dependent pruritic sensation in patients with AD. Moreover, air pollutants have been found to act on keratinocytes to produce artemin, leading to epidermal hyperinnervation and hypersensitivity to pruritus.⁷²

Another characteristic of pruritus in patients with AD is its chronicity. With chronic pruritus, scratching causes skin lesions, which in turn lead to activation of STAT3 in spinal dorsal horn astrocytes. Induction of lipocalin 2 by astrocytes sensitizes a pruritus-processing neuronal network involving GRPR⁺ spinal dorsal horn neurons, and thereby contributes to the vicious cycle of itching and scratching and to chronic pruritus (Fig 3).⁷³

Specific targets for pruritus

IL-31 and IL-31 receptor A. In human subjects and mice IL-31 is predominantly produced by T_H2 cells, and its receptor, IL-31 receptor A, is expressed on C-fibers.⁷⁴ Monthly injections of an anti-IL-31 receptor A antibody (CIM331; nemolizumab) significantly inhibited pruritus in patients with moderate-to-severe AD in a phase 2 clinical trial; at week 12, among the 216 patients who received nemolizumab every 4 weeks, changes in the pruritus visual analog scale were –43.7% in the 0.1-mg group, –59.8% in the 0.5-mg group, and –63.1% in the 2.0-mg group versus –20.9% in the placebo group ($P < .001$).⁷⁵ Although

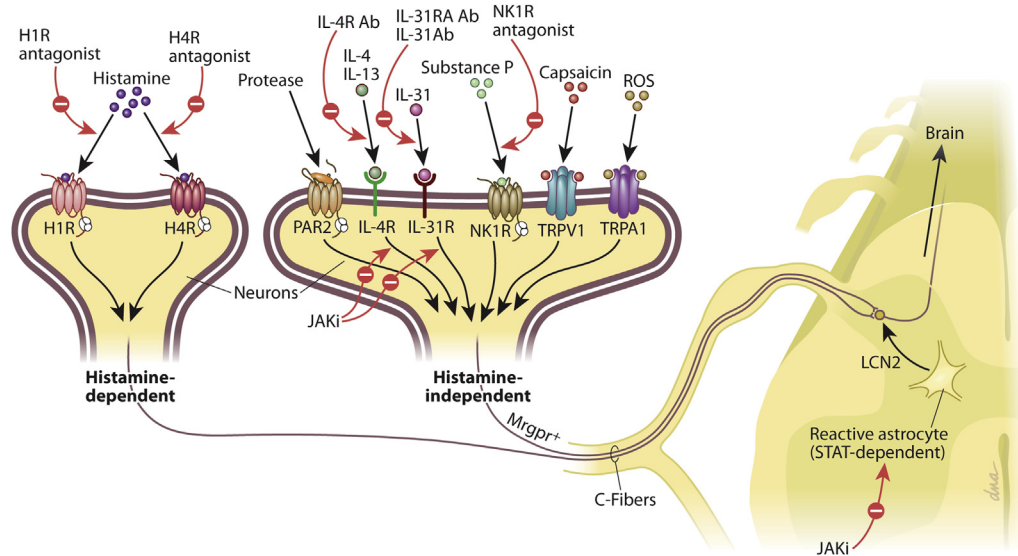


FIG 3. Mechanisms of pruritus. Each of the pruritogens involved in AD has its own specific receptor to induce itch. Both H1R⁺ histamine-dependent and Mas-related G protein-coupled receptor (Mrgpr)⁺ histamine-independent signaling pathways are thought to mediate pruritus in patients with AD. In the spinal dorsal horn STAT3-dependent reactive astrocytes produce lipocalin 2 (LCN2), which sensitizes a pruritic processing neuronal network involving GRPR⁺ neurons, leading to chronic pruritus. As shown in this figure, each antipruritus drug blocks each pruritic pathway. IL-4, IL-13, and IL-31 elicit their functions through JAK-STAT signaling. PAR2, Protease-activated receptor 2.

significant improvement in pruritus was seen by 3 days, the effect on AD severity by week 12 was low.⁷⁵ Use of nemolizumab was not associated with any serious adverse events.⁷⁵ Nemolizumab also increased sleep efficiency and decreased the use of topical hydrocortisone butyrate in the phase 2 clinical trial.⁷⁵ BMS-981164, an IL-31 neutralizing antibody, has completed a phase 1 clinical trial for AD.

Neurokinin 1 receptor. Plasma levels of the neuropeptide substance P are associated with disease activity of AD.⁷⁶ One of substance P's receptors is neurokinin 1 receptor (NK1R), and NK1R antagonists induced a reduction in scratch behavior in an AD mouse model.⁷⁷ Two NK1R antagonists (tradipitant, NCT02651714; and serlopitant, NCT02975206) are currently in phase II clinical trials for AD.

THE CUTANEOUS MICROBIOME: VILLAIN OR FRIEND?

Flares in patients with AD have been associated with a reduction in microbial diversity and increases in *Staphylococcus aureus*.⁷⁸ *S aureus* produces numerous factors that stimulate the immune response (most notably exotoxins) and worsen the epidermal barrier (eg, through expression of bacterial proteases and lipases and induction of keratinocyte serine proteases).⁷⁹ Bathing in dilute sodium hypochlorite (bleach, diluted to 0.005%) has become an easy maintenance intervention and has been thought to decrease the severity of AD from reduction in *S aureus*.⁸⁰ However, mechanistic studies have not shown a change in *S aureus* beyond that effected by concurrent topical corticosteroids⁸¹ and, rather, implicate an effect on inflammation⁸² and increased expression of barrier proteins.⁸³

The reduction in microbial diversity and not just the increase in *S aureus* has become a focus for potential therapeutics. Therapy with commensal bacteria has been the basis for fecal transplants in patients with *Clostridium difficile* gastrointestinal infection.

Indeed, a 5% lysate of the nonpathogenic bacterium *Vitroscilla filiformis* significantly reduced the severity and pruritus of AD, as well as transepidermal water loss and cutaneous colonization by *S aureus*, in a 2008 double-blind, randomized, placebo-controlled trial with 75 patients.⁸⁴ Since then, studies in mice and human subjects have supported the potential use of commensal strains as a nonantibiotic way to control pathogenic staphylococcal overgrowth, biofilm formation, or both. *Staphylococcus epidermidis* also has been found to activate Toll-like receptor 2, which increases antimicrobial peptides and tight junction barrier proteins. Recently, transplantation of commensal gram-negative rods from healthy volunteer skin, but not from patients with AD, enhanced barrier function, activated innate immunity, and controlled the growth of *S aureus* in a mouse model of AD.⁸⁵ Finally, commensal strains of coagulase-negative *S epidermidis* and *Staphylococcus hominis* from healthy patients have been applied to human AD skin and have been found to decrease colonization by *S aureus*.⁸⁶ Studies of the use of topically applied commensal organisms for AD are ongoing. These include spraying *Roseomonas mucosa*, a gram-negative coccobacillus, onto the arms of patients with AD (age ≥7 years; NCT03018275) and application of a Targeted Microbiome Transplant lotion containing coagulase-negative *Staphylococcus* to the arms of adults with moderate-to-severe AD (NCT03151148).

CONCLUSIONS AND FUTURE CONSIDERATIONS

Our improved understanding about the mechanism for development of AD is leading to an expanding pipeline of new and more targeted treatment interventions. In the past year, the first topical PDE4 inhibitor (crisaborole) and the first effective subcutaneously administered biologic (dupilumab) targeting the IL-4/IL-13 receptor have become available for mild-to-moderate and moderate-to-severe AD, respectively. Other topical, oral, and injectable medications in the pipeline are being developed to

suppress immune targets. The first biologic specifically targeting a cytokine causing itch (targeting the IL-31 receptor) has completed phase 2 trials, and vigorous research in understanding itch is uncovering other targets for small molecule inhibitors and biologics. Finally, an intriguing new principle in therapeutics is topically applying commensal organisms to AD skin and is showing promise in early human application. Although these emerging new therapies have the potential to revolutionize AD care, the extent of their effect on patient care will depend on their affordability and accessibility to patients with AD from a broad range of socioeconomic groups and with different insurance status.

To date, clinical trials are focused on finding more efficacious and safer therapies to combat the inflammation and itch of AD. However, there are 2 issues that are confounding trials. First, AD is commonly viewed as a single disorder, but there is heterogeneity based on the distribution and character of manifestations, severity, genetic risk factors (eg, having a mutation or mutations in *FLG*), and, as is becoming more obvious through biomarker analysis, expression patterns of immune activation. Current trial inclusion is based primarily on disease severity, raising the possibility that a test medication might be highly effective for a subset of affected subjects but that the number of these subjects within a test cohort is too low to detect significant improvement versus placebo overall. Although T_H2 pathway activation appears to be a universal trait of AD, the role of age, ethnicity/race, concomitant activation of other immune pathways, being deficient in *FLG* or other barrier components, one's microbiome, and other genetic and environmental factors in response to immune mediators is unclear and needs to be carefully considered as we move towards precision medicine. The other issue is the high rate of meeting the primary clinical end point of subjects treated with placebo in clinical trials. For all patients, the high placebo response is thought to reflect the intensive medical observation of trials and improved adherence to a regimen. For those with moderate-to-severe disease, a confounding factor is the frequent allowance of use of topical corticosteroids, given the tremendous pruritus and pain of stopping all treatment. Although allowing topical steroids increases recruitment and retention in trials, their use is likely to be greater in subjects receiving placebo with a poorer response to the test medication, further narrowing the gap between active and placebo treatment responses.

Finally, all of the treatments available to date for AD provide disease control, but patients desire interventions that can change the long-term course and ultimately "cure" the disease. In addition, interventions that prevent the onset of AD or the development of comorbidities, including the commonly associated allergic disorders, would be highly desirable, especially in families at higher risk. Recent studies have emphasized the important role of barrier dysfunction, as measured by increased transepidermal water loss, as early as 2 days of age in predicting the risk of AD in the first year of life²⁵ and food allergy by 2 years of age.⁸⁷ Indeed, early studies have suggested that daily application of emollients beginning in the neonatal period in high-risk infants reduces the risk of AD development.^{88,89} Current studies are exploring the protein and lipid barrier deficits of early AD and will guide future preventative intervention, but these studies emphasize the need to predict AD early and intervene prophylactically as early as the neonatal period. Similarly, studies of the microbiome in the

general population of infants have shown that colonization with commensal staphylococci at 2 months of age has been associated with a lower risk of having AD at 1 year of age,⁹⁰ suggesting the potential value of topical application of commensal bacteria as a preventive measure.

However, developing disease-modifying strategies once AD develops is the ultimate goal. Beyond short-term efficacy, long-term studies that test the persistence of effect of a systemic intervention once discontinued will be important, especially for patients with moderate-to-severe disease. Given the results of biomarker analyses in young children with early-onset AD, showing different immunophenotypes in blood versus adults with chronic disease,⁹¹ there might be a window of opportunity to alter the risk for later having other allergic comorbidities in addition to changing the course of the AD. Subphenotyping based on immunophenotypes, genomic patterns, and perhaps even one's microbiome⁹² will likely be required to optimally manage and change the course of the disease.

What do we know?

- Topical anti-inflammatory agents (eg, topical corticosteroids and calcineurin inhibitors) are often not sufficient to control more severe AD and can be associated with side effects, particularly if they are used inappropriately.
- Systemic immunosuppressants tend to be more effective than topical agents but are associated with numerous potential risks, are sometimes ineffective, and are inappropriate for long-term therapy.
- Targeted therapy based on understanding disease pathogenesis is expected to be more effective and have fewer side effects than broad immunosuppressants.
- Two recently released medications, a topical PDE4 inhibitor and an injectable IL-4 receptor mAb, are effective for mild-to-moderate and moderate-to-severe AD, respectively, with a good safety profile.

What is still unknown?

- To what extent activation of immune pathways in addition to T_H2 signaling contribute to AD pathogenesis
- Whether there are subphenotypes that respond selectively to more targeted topical and systemic medications
- Whether new medications directed against targets thought to drive AD will prove to be effective and without significant risk

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