REVIEW ARTICLE

A Therapeutic Renaissance – Emerging Treatments for Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic, inflammatory cutaneous disease that is characterized by complex immune dysregulation and skin barrier dysfunction with a wide variety of clinical phenotypes. Until recently, conventional therapeutic modalities for AD remained rather non-specific despite AD's complex etiology. Failing to take into account the underlying inflammatory pathways led to treatments with inadequate efficacy or unacceptable long-term toxicities. We are currently in the midst of a therapeutic renaissance in AD. Recent progress in molecular medicine provides us a better understanding of the AD pathogenesis, suggesting a dominant helper T cell (Th) 2/Th22 response with a varying degree of Th1/Th17 overexpression. Targeted therapeutic agents including biologics and small molecule inhibitors in development hold promises for more effective and safer therapeutic approaches for AD. A better understanding of individual differences amongst AD patients will allow for a more tailored approach in the future. This review aims to cover the most promising emerging therapies in the field of atopic dermatitis utilizing recently published manuscripts and up-to-date conference abstracts and presentations.

SIGNIFICANCE

Effective treatment of atopic dermatitis is complicated due to its chronic nature, multifaceted pathophysiology, and variable clinical manifestations. The success of dupilumab confirms the importance of type 2 cytokines in the pathophysiology of atopic dermatitis. Besides type 2 cytokines, certain phenotypes of atopic dermatitis may be driven by additional cytokine pathways. However, data to date attempting to target specific cytokines outside of the type 2 axis have been largely unsuccessful. Further data using large-scale and long-term clinical trials are needed in order to create tailored and personalized treatments for atopic dermatitis.

With an increasing prevalence worldwide, atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that often presents in infancy and may persist or re-emerge in adulthood (1). The pathophysiology of AD is complex and involves genetic predispositions, environmental factors, skin barrier dysfunction, immune dysregulation, and disruptions in the skin microbiota (2, 3). Approximately one third of all AD patients have moderate-to-severe disease with symptoms including pruritus, increased risk of sleep disturbances, mental health comorbidities, and suicidal ideation, all of which contribute to a poor quality of life (QoL) (4, 5). Selecting treatments for AD in the clinical setting is often challenging due to a variety of AD phenotypes, which may be due to the various cytokine profiles of AD (6). Conventional systemic immunosuppressive agents including corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil provide inadequate long-term control in many patients who require systemic therapy due to inadequate efficacy or adverse drug reactions. Thus, there remains a large unmet need for an effective and safe long-term systemic treatment for AD. Considering the multifactorial etiology of AD, the ideal therapeutic treatment should target the specific molecular defect or defects underlying the particular patient's disease. Over the past few years, our increasing knowledge of the immunopathogenesis and heterogeneity of AD has initiated an era of targeted therapeutics, such as biologics and small molecule inhibitors. We can expect to see a more personalized therapeutic treatment approach for AD in the future.

PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

Analysis of the skin and blood of patients with AD reveal an array of adaptive and innate immune derangements. For many years, AD pathophysiology was thought to be driven by a predominant helper T (Th) 2 response in the acute phase of the disease, and a skewed Th1 response in the chronic phase (7). This acute (Th2) and chronic (Th1) paradigm emerged from studies involving inhalant allergen patch tests – an artificial model system with questionable relevance to AD. In this model, Th2 cells and interleukin (IL)-4 messenger RNA (mRNA) were predominantly observed in acute lesions, while Th1 cells and recombinant interferon (IFN)-γ mRNA were prima-

rily seen in chronic lesions (8). Recent findings using patients with AD, not patch tests, have suggested that AD has a stronger association with a Th2/Th22 response and a much more variable Th1/Th17 response throughout both the acute and chronic stages of the disease (9–11). In the acute phase, lesions display overactivation of Th2/Th22 related signals and to a lesser degree Th17 related signals (12, 13). Intensification of these axes, along with an upregulation of Th1 cells, recruit and coordinate the chronic phase of the disease (9).

In AD skin, disruption of the epidermal barrier by irritants, allergens, and pathogens give rise to the activation of nonlymphoid cells like Langerhans cells (LC) and keratinocytes. Epidermal disruption may also occur via genetically driven alterations in skin barrier function such as loss-of-function mutations in the *FLG* gene that encodes for the skin barrier protein filaggrin (14). Disrupted keratinocytes initiate or potentiate inflammation via the release of cytokines and chemokines, including thymus- and activation-regulated chemokine (TARC), thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. These cytokines drive local tissue inflammation and activate a series of Th2-mediated events such as immunoglobulin (Ig) E class switching and recruitment of IL-5 dependent eosinophils into the skin (**Fig. 1**) (15, 16). Th2 cells release IL-4, IL-5, IL-13, and IL-31, which mediate the activation of additional inflammatory cells like mast cells and eosinophils. They also inhibit the expression of barrier proteins such as filaggrin, and barrier lipids such as ceramides (17, 18). Notably, IL-4 and IL-13 induce keratinocytes to secrete additional TSLP, which results in Th2 polarization and a positive feedback loop (19). IL-31, an interleukin that induces itching via sensory nerves, is upregulated in AD lesions and triggers scratching behavior, which may further drive inflammation (20). Group 2 innate lymphoid cells (ILC2s), which

are activated by keratinocyte mediators, release both IL-5 and IL-13 that perpetuates Th2 immunity (21, 22). In conjunction with IL-17 released by Th17 cells, IL-22 released by Th22 cells promotes epidermal hyperplasia and aberrant epidermal differentiation (9).

By identifying a growing number of immune pathways underlying AD, numerous targeted and broad-acting drugs are currently in the therapeutic pipeline. Given the critical role of the Th2 axis in AD, anti-Th2 agents like dupilumab, which represents the first biologic drug approved for AD, have been developed (23, 24). Multiple targeted drugs involving the Th22 and Th17 pathways, as well as broader T cell inhibitors, are also currently under investigation. The aim of this review is to provide up to date information regarding this unique and promising era of innovation and novel therapeutic development.

CLINICAL AND MOLECULAR HETEROGENEITY OF ATOPIC DERMATITIS

Recent research reveals several AD subtypes classified by different endotypes and phenotypes including age, chronicity, ethnicity, filaggrin gene mutational status, IgE status, *S. aureus* colonization status, and underlying molecular signaling abnormalities (25–28). Subtypes of various ethnic backgrounds such as European American decent, African American decent, and Asian origin have also been identified. Other AD classifications include pediatric patients versus adult patients, subjects with acute versus chronic disease, and patients exhibiting intrinsic versus extrinsic type. In spite of a similarity in clinical presentation and response to therapy, extrinsic AD was historically defined as patients with high serum IgE levels, personal and family atopic background, while the intrinsic phenotype having normal IgE levels shows female predominance and lack any other atopic diathesis (25).
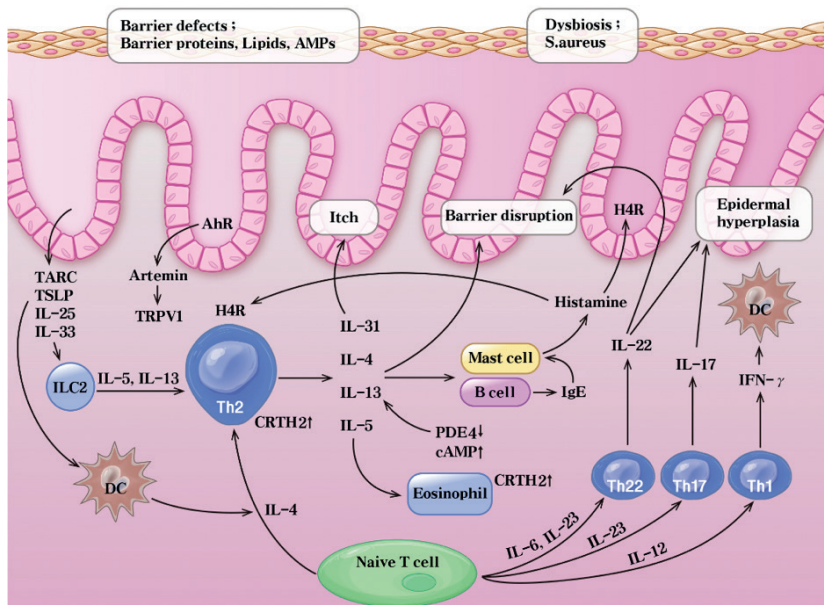
Fig. 1. Immune pathophysiology of atopic dermatitis (AD). In AD skin, epidermal disruption initiates or potentiates inflammation through the release of cytokines and chemokines, including thymus- and activation-regulated chemokine (TARC), thymic stromal lymphopoietin (TSLP), interleukin (IL) -25, and IL-33. These cytokines drive local tissue inflammation and activate a series of Th2 cytokines such as IL-4, IL-5, IL-13, and IL-31, thereby leading to immunoglobulin (Ig) E class switching and accumulation of inflammatory cells into the skin. Together with IL-17 released by Th17 cells and IL-22 released by Th22 cells, epidermal hyperplasia and barrier disruption are intensified throughout the acute and chronic stages of AD. AD: atopic dermatitis; Th: helper T; AMPs: antimicrobial peptides; AhR: aryl hydrocarbon receptor; ILC2: group 2 innate lymphoid cells; TRPV1: transient receptor potential cation channel subfamily V member 1; H4R: histamine receptor type 4; DC: dendritic cell; CRTH2: chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes; PDE4: phosphodiesterase4; cAMP: cyclic adenosine monophosphate; IFN-γ: interferon-γ.

Despite a strong polarization of Th2/Th22 identified in the general AD population, there appears to be a relatively dominant Th17 subtype in pediatric patients, patients of Asian descent, and patients with intrinsic AD. African-American patients with AD and pediatric patients with AD also appear to lack any Th1 activation (25). A Dutch study based on the analysis of serum biomarkers of 193 adult patients with moderate-to-severe AD identified 4 endotype clusters of AD (29). Clusters 1 and 4 show higher levels of Th2 cytokine expression in "erythematous" phenotypes, while clusters 2 and 3 show lower levels of Th2 cytokine expression in "lichenified" phenotypes. Although further studies are needed to confirm the reliability of these subtypes, these findings and others can serve as useful tools in developing targeted treatments for AD. The clinical relevance of emerging endotypes will be deemed clinically relevant if they identify patients that respond better to a particular therapeutic (i.e., precision medicine) or help predict the natural course.

TOPICAL THERAPIES

Despite the advent of new systemic agents, topical therapies are still an essential component in the management of AD. Topical anti-inflammatory therapies for AD include the use of topical corticosteroids (TCS) as first-line therapy with topical calcineurin inhibitors (TCI) as an alternative to TCS in areas where TCS use is not recommended. Moderate-to-severe patients with AD, however, are often inadequately controlled with these agents. Additionally, the prolonged use of TCS may cause telangiectasia, skin atrophy, dyschromia, and adverse events. The use of TCI is often limited by burning and stinging (30). Given these limitations in traditional topical therapies, there remains a significant unmet need for patients. New topical agents are now being studied to modulate phosphodiesterase (PDE) 4, Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, aryl hydrocarbon receptor (AhR), and the skin microbiome (**Table I**).

PDE4 inhibitors

Hanifin and colleagues (31) first made the observation that AD monocytes display overactive phosphodiesterase enzyme activity. Inhibition of PDE4 leads to an increase in cyclic adenosine monophosphate (cAMP), resulting in the down-regulation of inflammatory cytokines in chronic inflammatory skin diseases such as psoriasis and AD (32). Crisaborole, a topical PDE4 inhibitor was first approved in 2016 by the US Food and Drug Administration (FDA) for patients with mild-to-moderate AD over the age of 2 years. Two phase III trials showed

Table I. Novel topical targeted therapies of AD (in or beyond phase II trial)

Target	Agent	Mechanism	Phase status	Clinical trials
Phosphodiesterase 4 (PDE4)	Crisaborole/AN2728	PDE4 inhibitor	I/II completed	NCT01652885
			II completed	NCT03233529
				NCT01602341
			II completed	NCT03954158
			III completed	NCT02118766
				NCT02118792
			III ongoing	NCT04040192
			IV ongoing	NCT03868098
				NCT03539601
	MM36/OPA-15406	PDE4 inhibitor	II completed	NCT02945657
				NCT02068352
				NCT02914548
				NCT03018691
			III ongoing	NCT03961529
			III completed	NCT03911401
				NCT03908970
	Roflumilast	PDE4 inhibitor	II completed	NCT01856764
				NCT03916081
	AN2898	PDE4 inhibitor	II completed	NCT01301508
	Lotamilast/RVT-501/E6005	PDE4 inhibitor	I/II completed	NCT01179880
				NCT02094235
			II completed	NCT01461941
				NCT02950922
				NCT03394677
	DRM02	PDE4 inhibitor	II completed	NCT01993420
	LEO29102	PDE4 inhibitor	II completed	NCT01037881
Janus kinase (JAK)	Tofacitinib	JAK 1/3 inhibitor	II completed	NCT02001181
	Delgocitinib/JTE-052/LEO124249	JAK 1/3 inhibitor	IIa completed	NCT01037881
	Ruxolitinib/INCB18424	JAK 1/2 inhibitor	II completed	NCT03011892
			III ongoing	NCT03745651
				NCT03745638
Aryl hydrocarbon receptor (AhR)	Tapinarof/ WBI-1001/benvitimod/ GSK2894512	AhR agonist	I/II completed	NCT00837551
			II completed	NCT02564055
				NCT01098734
S. aureus	Roseomonas mucosa bacteria	Commensal interaction	I/II completed	NCT03018275
	Coagulase-negative Staphylococcus	Commensal interaction	I/II completed	NCT03151148
			II ongoing	NCT02144142

significant efficacy with 51% clear and 48% almost clear in the Investigator's Static Global Assessment (ISGA) score (33). A large vehicle effect, however, leads to a relatively large number needed to treat (NNT), ranging between 8 and 14. (34). This translates to between 8 and 14 patients are needed to be treated before one person achieves success over vehicle treatment (35). Improved signs of pruritus and good drug tolerability were reported amongst patients. Limited adverse events included pain, burning, and stinging. However, the clinical prevalence of these events are seemingly more common in clinical practice than that reported in trials. A study of crisaborole over 48 weeks confirmed its safety for longer-term use (36) but comparative efficacy data with other topical agents is currently lacking. A new study has been initiated to evaluate the efficacy of crisaborole compared to other topical agents like TCS and TCI (NCT03539601). MM36 (OPA-15406), another PDE4 inhibitor with high selectivity for PDE4B, at higher concentration showed significant improvement in Eczema Area and Severity Index (EASI) score at week 1 compared to placebo and persisted for 8 weeks (37). Various PDE4 inhibitors including roflumilast, AN2898, lotamilast, DRM02, and LEO29102 are currently undergoing phase II and phase III trials. Overall, topical PDE4 inhibitors appear to be a safe approach to long-term management of selected mild-to-moderate AD without the potential for significant systemic absorption or cutaneous atrophy.

JAK and other kinase inhibitors

JAK inhibitors are small molecules that inhibit the JAK-STAT signaling pathway. Although they have been mostly studied as systemic therapeutics for AD, topical applications have also shown promise in clinical trials. The JAK -STAT pathway has been implicated in the signaling of multiple AD-related cytokines such as IL-4, IL-5, IL-6, IL-12, IL-13, IL-22, IL-23, IL-31, IL-33, and IFN-γ (38–40). A JAK family of 4 receptor associated kinases (JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2) phosphorylate intracellular receptors and increase the production of a group of STATs, leading to the activation of targeted gene expression (**Fig. 2**). JAK inhibitors target different combinations of kinases with variable selectivity, resulting in overlapping but distinct inhibitory effects on various cytokine pathways. Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase involved in the release of pro-inflammatory cytokines including IL-17, B cell activation, and keratinocyte differentiation (40). The SYK pathway plays an important role in Th17 signaling by recruiting Th17 cells to the skin along with inducing the production of CCL (C-C motif chemokine ligand) 20 (41). Consequently, targeting the JAK-STAT and SYK pathways downregulates multiple immune axes involved in the pathogenesis of AD (Th1, Th2, Th17, and Th22). The broader immune modulation of JAK inhibition holds the potential to bring greater ef-
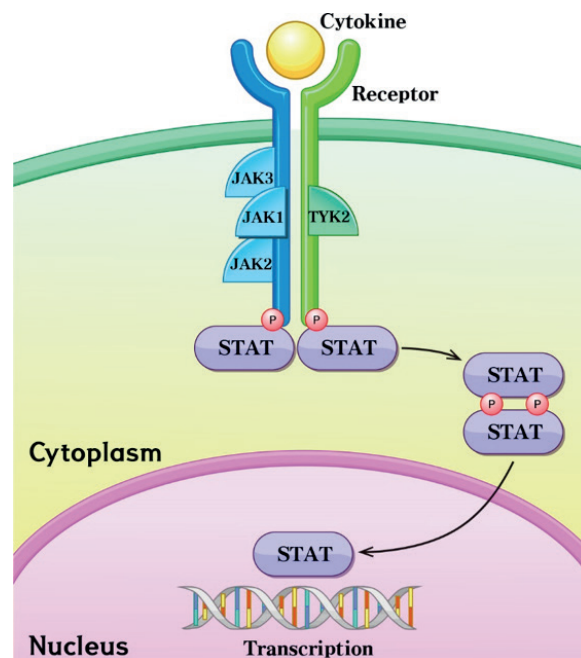
Fig. 2. JAK-STAT pathway. A cytokine binds to its cell surface receptor. A Janus kinase (JAK) family of four receptor associated kinases (JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2) phosphorylate intracellular receptors and increase the production of a group of signal transducer and activator of transcription (STAT). Phosphorylated STATs dimerize and translocate to the nucleus, leading to the activation of targeted gene expression.

ficacy. However, this theoretically results in an increase in potential adverse events as well.

Topical JAK inhibitors decrease IL-4 and IL-13 signaling pathways and enhance skin barrier functions in mouse AD models (42). A phase IIa trial investigating tofacitinib, a potent JAK1/JAK3 inhibitor, for patients with mild-to-moderate AD showed significant reduction of pruritus by day 2 and a large reduction in EASI score by week 4 (81% vs. 29% (placebo), $p < 0.001$) (43). The application site reactions reported in two subjects were mild pain or mild pruritus. A controlled study of delgocitinib (JTE-052/LEO 124249), a pan JAK (JAK1-3,TYK2) inhibitor, showed significant improvement in the overall symptoms of AD by week 4, and low modified EASI (mEASI) and Investigator's Global Assessment (IGA) scores with a favorable safety profile (44). Improvements in pruritus were also observed by day 1, which was likely due to the inhibition of IL-31 signaling mediated by the JAK-STAT pathway (20) or possibly via direct effect of JAK inhibition on itch transmission by neurons (45). Improvements in mEASI score with the higher doses of delgocitinib were similar to the tacrolimus 0.1% ointment active control arm, although there was no statistical comparison (44). In an ongoing phase II trial, topical ruxolitinib (INCB018424), a potent JAK1/JAK2 inhibitor, showed significant efficacy in EASI score at week 4 in the cream 0.5% and 1.5% arms versus vehicle (46). Topical ruxolitinib at higher doses (1.5%) showed greater improvements in EASI score at week 4 than triamcinolone cream 0.1%. Other JAK inhibitors such as cerdulatinib (RVT-502), a

dual JAK and SYK inhibitor, and SNA-125, a JAK 3 and tropomyosin receptor kinase A (TrkA) inhibitor, are currently being evaluated in phase I/II trials of AD, however no data are available for review at this time.

AhR agonist

The AhR is a cytosolic ligand-activated transcription factor that is involved in both pro- and anti-inflammatory signaling pathways (47). It has the potential to impact the balance of Th17 and regulatory T (Treg) cell production and can restore epidermal barrier function (48, 49). Tapinarof (benvitimod/GSK2894512/WBI-1001), an AhR agonist, is a naturally derived molecule produced by the bacterial symbionts of entomopathogenic nematodes (50). In two phase II trials, significant improvements in EASI and IGA scores were seen at week 4 in patients with mild-to-moderate AD and significant efficacy in IGA scores of both 0.5% and 1% dosing groups at week 6 in patients with mild-to-severe AD (51, 52). In earlier studies of higher dose tapinarof at 2%, headache, diarrhea, nausea and/or vomiting were observed. This suggests the potential for systemic absorption at higher concentrations (53). Phase 3 studies are anticipated.

Commensal organisms

Cutaneous dysbiosis, characterized by a reduction in microbial diversity and an increase in colonization of *S. aureus,* has been shown to initiate and worsen the flare of AD (54). Recent research suggests a unique phenotype and endotype for patients colonized with *S. aureus*. Characteristics of *S. aureus*-colonized patients include more severe skin disease, reduced barrier function, increased serum lactate dehydrogenase (LDH) levels, increased allergen sensitization, elevated IgE levels, elevated eosinophil counts, and increased levels of various Th2 biomarkers such as TARC, periostin, and CCL26 (55). Increased *S. aureus* colonization has been proposed as a potential mechanism for disease progression and flare-up of AD. A recent open-label trial with topical application of *Roseomonas mucosa* for patients with AD found that the commensal bacterium provided patients with clinical improvement in AD severity and pruritus, and a reduction of TCS use (56). Another study reported that autologous transplantation of coagulase-negative *Staphylococci* enriched with novel anti-*S. aureus* peptides leads to a decrease in *S. aureus* colonization and clinical improvements in AD (57). Currently, a phase I/II trial using *Roseomonas mucosa* and a phase II trial testing coagulase-negative *Staphylococcus* are underway. These studies will help elucidate whether the dysbiosis in AD is a primary driver of the disease or merely a consequence of barrier dysfunction or type 2 inflammation. Should this approach provide efficacy, it is intriguing to speculate that transplanting beneficial live commensals could theoretically yield a remittive effect on the disease.

SYSTEMIC THERAPIES

Systemic treatments may be appropriate for pediatric and adult patients with moderate-to-severe AD whose disease is inadequately controlled with appropriate amounts of topical therapies. According to an International Eczema Council (IEC) consensus paper, the decision to commence or offer systemic treatments should involve an assessment of disease severity, an understanding of the impact on QoL, and include individual factors such as patient preferences, prior treatment history, financial considerations, and co-morbidities (58). Traditionally, systemic therapies include phototherapy or systemic immunomodulators such as corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil. Given the risk of potential toxicities with traditional immunosuppressant long-term treatments, there is still an unmet need for safe and effective long-term therapies. Dupilumab, the first biologic drug approved for AD, has filled this large void for a safe and effective therapy for long-term use. Since the advent of dupilumab, a number of biologics and small molecule inhibitors are now being developed and investigated to provide alternatives to dupilumab (**Table II**).

Targeting Th2 pathway

IL-4 and/or IL-13 antagonists. IL-4 and IL-13 are the key mediators of Th2 inflammatory responses and are responsible for the production of IgE. Cell culture studies reveal increased IL-4/IL-13 levels that not only lead to the recruitment of additional inflammatory cells, but also disturb skin barrier function by inhibiting the production of barrier structural proteins like filaggrin, lipids and antimicrobial peptides, and encourage *S. aureus* colonization (57, 59). IL-13 is overexpressed in both lesional and non-lesional AD, and correlates with disease severity (10, 60). Dupilumab, a fully human monoclonal antibody (mAb), inhibits both the IL-4 and IL-13 signaling pathway by blocking their shared IL-4Rα receptor subunit (61). Dupilumab was approved to treat moderate-to-severe AD in adults in the US and Europe in 2017, and its approval was extended to patients with moderate-to-severe AD over the age of 12 years in the US in 2019 (62). In a phase III trial of identical design (SOLO1 and SOLO2), adult patients with moderate-to-severe AD who received dupilumab every other week showed improvement in disease at week 16, with the proportion of patients achieving a 75% reduction in EASI score (EASI-75) ranging between 44–51% versus placebo (12–15%) (24). Patients also reported improvements in their symptoms including pruritus, anxiety, and depression. They also reported an overall improvement in QoL. In another phase III study (LIBERTY AD CHRONOS), a year-long trial of dupilumab showed an improved disease activity with a good safety profile when combined with TCS exhibiting only local injection reactions and conjunctivitis as adverse events (63). A LIBERTY AD CAFÉ study with concomi-

Table II. Novel systemic targeted therapies of atopic dermatitis (AD) (in or beyond phase II trial)

Target	Agent	Mechanism	Route	Phase status	Clinical trials
Biologics					
T-helper 2	Dupilumab	Anti-IL-4Rα mAb	Subcutaneous	IV ongoing	NCT03411837
					NCT03293030
					NCT03389893
					NCT03667014
	Pitrakinra/Aeroderm	Anti-IL-4 mAb	Subcutaneous	IIa completed	NCT00676884
	Lebrikizumab	Anti-IL-13 mAb	Subcutaneous	II completed	NCT02340234
					NCT03443024
					NCT02465606
					NCT04178967
				III ongoing	NCT04146363
	Tralokinumab	Anti-IL-13 mAb	Subcutaneous	II completed	NCT02347176
					NCT03562377
				III completed	NCT03363854
					NCT03160885
					NCT03131648
				III ongoing	NCT03587805
					NCT03761537
					NCT03526861
	Tezepelumab/AMG157/ MEDI9929	Anti-TSLP mAb	Subcutaneous	IIa completed	NCT02525094
				II ongoing	NCT03809663
	GBR830	Anti-TSLP mAb	Subcutaneous	II completed	NCT02683928
				IIb ongoing	NCT03568162
	KHK4083	Anti-OX40 mAb	Subcutaneous	II ongoing	NCT03703102
	Nemolizumab/CIM331	Anti-IL-31RA mAb	Subcutaneous	II completed	NCT01986933
					NCT03100344
				II ongoing	NCT03921411
				III ongoing	NCT03989206
					NCT03985943
					NCT03989349
	Mepolizumab	Anti-IL-5 mAb	Intravenous	II terminated	NCT03055195
T-helper22	Fezakinumab/ILV-094	Anti-IL-22 mAb	Subcutaneous	II completed	NCT01941537
T-helper 1/ T-helper 17	Ustekinumab	Anti-IL-12/23p40 mAb	Subcutaneous	II completed	NCT01806662
					NCT01945086
	Secukinumab	Anti-IL-17A mAb	Subcutaneous	II completed	NCT02594098
					NCT03568136
	MOR106	Anti-IL-17C mAb	Subcutaneous	II terminated	NCT03568071
					NCT03864627
IgE	Omalizumab	Anti-IgE mAb	Subcutaneous	II completed	NCT01179529
				IV completed	NCT02300701
					NCT00822783
	Ligelizumab/QGE031	Anti-IgE mAb	Subcutaneous	II completed	NCT01552629
Interleukin (IL)-1α	Bermekimab/MABp1	Anti-IL-1α mAb	Subcutaneous	II completed	NCT03496974
				II ongoing	NCT04021862
Small molecules					
Janus kinase (JAK)	Barcitinib	JAK1/2 inhibitor	Oral	II completed	NCT02576938
				III completed	NCT03334422
					NCT03733301
					NCT03334396
				III ongoing	NCT03559270
					NCT03435081
					NCT03334435
					NCT03428100
					NCT03952559
	Upadacitinib/ABT494	JAK1 inhibitor	Oral	II completed	NCT02925117
				III ongoing	NCT03607422
					NCT03569293
					NCT03568318
					NCT03738397
					NCT03661138
	Abrocitinib/PF-04965842	JAK1 inhibitor	Oral	II completed	NCT02780167
				II ongoing	NCT03915496
				III completed	NCT03349060
					NCT03575871
					NCT03627767
					NCT03422822
				III ongoing	NCT03720470
					NCT03796676
	ASN002/Gusacitinib	JAK/spleen tyrosine kinase inhibitor	Oral	II completed	NCT03531957
				II terminated	NCT03654755
Phosphodiesterase (PDE) 4	Apremilast	PDE4 inhibitor	Oral	II completed	NCT02087943
					NCT00931242
Chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes (CRTH2)	OC000459/ODC-9101	CRTH2 mAb	Oral	IIa completed	NCT02002208
	Fevipiprant/QAW039	CRTH2 mAb	Oral	IIb completed	NCT01785602
Histamine receptor	ZPL-389	H4R inhibitor	Oral	II completed	NCT02424253
				II ongoing	NCT03948334
					NCT03517566
Neuropeptide substance P and neurokinin 1 receptor (NK1R)	Tradipitant/VLY-686	NK1R inhibitor	Oral	II completed	NCT02651714
				III completed	NCT03568331
				III ongoing	NCT04140695
	Serlopitant/VPD-737	NK1R inhibitor	Oral	II completed	NCT02975206
				III ongoing	NCT03540160

tant use of TCS exhibited an EASI-75 of 63% at week 16 in moderate-to-severe adult AD who were refractory or intolerant to cyclosporine (64). Translational studies reveal that dupilumab reduces expression of Th2 immunity markers, Th17/Th22-related epidermal hyperplasia, and inflammatory cell infiltrates. It also enhances the expression of genes that control epidermal differentiation and barrier function, including genes for loricrin and filaggrin (65). Two meta-analyses demonstrated statistically significant increased efficacy and a well-tolerated safety profile for patients with moderate-to-severe AD on dupilumab compared to placebo (66, 67).

Dupilumab-induced conjunctivitis, or ocular surface disease, is a common (5–28% of patients) but poorly understood side effect (68). The conjunctivitis is usually mild to moderate in severity and can be treated with various topical anti-inflammatory approaches. For unknown reasons, the conjunctivitis associated with dupilumab therapy only occurs in patients with AD. This side effect was not observed in studies of asthma or chronic sinusitis (24). Ongoing mechanistic studies will hopefully shed light onto the etiology of this adverse effect.

Overall, dupilumab appears to be a safe therapy suitable for long-term use. Dupilumab does not appear to be immunosuppressive and has not been associated with increased overall infection rates. Studies reveal significantly reduced risk of serious or severe infections and bacterial non-herpetic skin infections compared to placebo (69). Dupilumab appears to correct AD skin dysbiosis – perhaps the mechanism that explains the observed protection against skin infections (65). Vaccination responses are also not affected by dupilumab therapy (70). No laboratory monitoring is required as no end-organ damage has been observed (70, 71). Dupilumab was also recently approved by the FDA for moderate-to-severe asthma with eosinophilic phenotype or oral corticosteroid-dependent asthma and chronic rhinosinusitis with nasal polyposis that are also driven by type 2 cytokines (62). Pitrakinra (Aeroderm), a biologic that targets only IL-4, has been tested in a phase IIa trial. However, no results have been reported and the status of further development is unknown.

IL-13 antagonists. IL-13 plays an important role in allergic inflammation and is expressed in both acute and chronic lesions of AD (72). Like IL-4, IL-13 induces keratinocyte to produce CCL26, thereby causing an accumulation of eosinophil at the inflammatory lesion (73). Lebrikizumab, an anti-IL-13 mAb, at 125 mg dose every 4 weeks achieved an 50% reduction in EASI score (EASI-50) of 82% at week 12 as compared to a placebo group response of EASI-50 of 62% at week 12 for patients with moderate-to-severe AD with concomitant mandatory TCS use twice daily ($p = 0.026$) (74) in a placebo-controlled phase II trial (TREBLE). In a recent press release from a phase IIb trial, patients treated with lebrikizumab at the 125 mg dose every 4 weeks and at

the 250 mg dose every 2 or 4 weeks showed significantly dose- and frequency-dependent improvements in EASI scores compared to placebo at 16 weeks (75). Tralokinumab, another anti-IL-13 mAb, showed significant improvement in EASI and IGA scores in a phase II study, particularly in patients with high serum biomarker levels of IL-13 activity (76). Heavy use of concomitant TCS likely diminished the effect size when compared to placebo. Patients reported improvement in QoL and pruritus, and there were no significant adverse effects. A phase III trial (NCT03131648) using tralokinumab monotherapy without TCS is underway to better evaluate its efficacy. Overall, IL-13 inhibitors appear to be well tolerated and show an acceptable safety profile with limited adverse events, including upper respiratory infections (URIs), nasopharyngitis, and headaches that are common but mild and self-limited (74, 76). Phase III data will be important to reveal whether conjunctivitis is an IL-13 class effect or is limited to only certain biologics targeting the pathway.

Inhibitors of the TSLP-OX40 axis. The TSLP-OX40 axis is also known to play an important role in initiating the Th2 allergic inflammatory response (77). Keratinocyte-derived TSLP activates dendritic cells to induce the production of Th2 immunity cytokines such as IL-4, IL-5, IL-13, and tumor necrosis factor (TNF)-α (19). IL-33 appears to amplify TSLP's effect of inducing expression of OX40 ligand on dendritic cells (78, 79). Tezepelumab (AMG157/MEDI9929), an anti-TSLP mAb, is regarded to be a potential suppressor of the Th2 pathway. In a phase IIa trial (NCT02525094), however, it did not show a significant EASI-50 response compared to placebo at week 12 in patients with moderate-to-severe AD, presumably due to heavy concomitant TCS use in the placebo group (80). In a phase IIa trial, GBR 830, an anti-OX40 mAb, was well tolerated and showed an acceptable safety profile, decreased inflammatory serum biomarkers, and significant improvement in EASI-50 versus placebo (81). In a phase I trial (NCT03096223), patients treated with KHK4083, an anti-OX40 mAb, every 2 weeks for 6 weeks showed a continuous reduction in EASI score even at week 22 suggesting a long-lasting response (82). An additional phase II trial (NCT03703102) is underway. Currently, there have been several proof-of-concept (PoC) trials testing various TSLP-OX40 axis-related inhibitors including a TSLP receptor antagonist MK-8226 (NCT01732510), an anti-IL33 mAb Etokimab (ANB020) (NCT03533751).

IL-31 receptor antagonists. Interruption of the itch-scratch cycle is one of the main goals in managing AD. IL-31, dubbed the "itch cytokine" is predominantly produced by activated Th2 cells and mast cells. The IL-31 receptor (IL-31R) is expressed on C-fibers of peripheral neurons (83). IL-31 is significantly increased in acute and chronic AD and plays a critical role in pruritus and disease activity (84). Nemolizumab, an anti-IL-31RA

mAb, showed a significant reduction in visual analogue scale (VAS) scores for pruritus in patients with moderate-to-severe AD in a 12-week phase II trial (85). In another long-term phase II trial, it showed significant and continued itch suppression and was well-tolerated over the 64 weeks trial with limited adverse events, including nasopharyngitis, AD exacerbations, and URIs (86). A recent phase IIb trial revealed that nemolizumab significantly improved EASI, IGA and itch scores at week 24 versus placebo and was well tolerated, with the 30 mg dose being most effective (87). BMS-981164, an anti-IL-31 mAb, was completed as a phase Ib trial (NCT01614756), but results have not yet been published. KPL-716 is an anti-oncostatin M receptor beta mAb (anti-OSMRβ) inhibiting both IL-31 and oncostatin M, an inflammatory signal implicated in pruritus, Th2 inflammation, and fibrosis. KPL-716 showed good safety and tolerability as well as an anti-pruritic effect in patients with moderate-to-severe AD in a phase Ia/Ib study (88). Additional phase II studies (NCT03858634, NCT03816891) for chronic pruritic diseases and prurigo nodularis are currently underway.

IL-5 antagonist. Eosinophils are speculated to play a large role in the pathogenesis of AD due to their high prevalence in tissue and blood found throughout the course of the disease. IL-5 induces the migration of eosinophils within inflamed tissue of patients with Th2 allergic inflammatory diseases like asthma and eosinophilic esophagitis (89). Mepolizumab, an anti-IL-5 mAb recently approved for severe eosinophilic asthma, was tested in a pilot study for AD but did not reach statistical significance in SCORing Atopic Dermatitis (SCORAD) score, pruritus scoring, and TARC levels despite decreasing the peripheral blood eosinophilic count (90). Given its efficacy in treating eosinophilic asthma, a phase II trial for moderate-to-severe AD had been implemented to test the effectiveness in the AD subtype with eosinophilia but was terminated early, as this study reached pre-determined futility criteria following interim analysis.

Targeting Th22 pathway

IL-22 promotes epidermal hyperplasia and disrupts barrier function by inhibiting keratinocyte differentiation and tight junction production (91). IL-22 is significantly increased in AD lesions and expression levels correlate with disease severity (60). In a phase II trial funded by the National Institutes of Health, fezakinumab, an anti-IL-22 mAb, did not reach significance in reducing the SCORAD score compared to placebo, but a sub-analysis of severe AD (SCORAD score >50) showed significant improvement with fezakinumab versus placebo (92). It was overall well-tolerated with a limited safety profile, including URIs as adverse events. A recent study revealed fezakinumab had a better efficacy in patients with a higher IL-22 baseline, suggesting an effect of IL-22

blockade on multiple inflammatory pathways encompassing Th1, Th2, Th17, and Th22 axis (93). Treatment antagonizing IL-22 could be a promising option amongst African American, Asian, intrinsic, and pediatric AD subtype patients showing dominant Th22 polarization and/or psoriasiform Th17/Th22 endotypes (25).

Targeting Th17 pathway

Some phenotypes such as Asian, intrinsic, pediatric, and elderly AD show higher expression of Th17-related markers like those found in psoriasis (25). Thus, these patients may be potential candidates for IL-17/IL-23 targeting therapies. IL-23 initiates both Th17 and Th22 pathways and is significantly decreased after AD treatments (94). The IL-17 family consists of 6 members of interleukins, IL-17A-F. Among them, IL-17A and IL-17C show complementary cooperation between keratinocytes and T cells, leading to the amplification of cell immune responses (95). Unlike IL-17A which is produced by Th17 cells and innate immune cells, IL-17C appears to be a keratinocyte-derived cytokine (96). Despite showing promise in several reports of AD (97, 98), ustekinumab, a mAb antagonizing IL-12/IL-23p40 with efficacy in psoriasis, did not demonstrate significant improvements over placebo with concomitant TCS use in a phase II trial for AD (99). In another phase II trial in Japan, patients with severe AD treated with ustekinumab 45 mg and 90 mg did not show meaningful efficacy versus placebo, although it was generally well-tolerated (100). MOR106, an anti-IL-17C mAb, exhibited an EASI-50 of 83% at week 4 at the higher dose and the treatment response maintained over 2 months after stopping treatment in a phase I trial (NCT02739009) (101). MOR106 and secukinumab, an anti-IL-17A mAb, are being tested for AD in phase II trials.

IgE antagonists

IgE is a hallmark for atopic diseases and is a downstream product of the Th2 axis. It is implicated in basophilic activation and the initiation of sensitization in allergic inflammatory cascades. IgE is also present on the cell surface of inflammatory dendritic cells (IDECs) characteristic of AD (102). Extrinsic AD subtypes defined by high levels of IgE and pediatric AD subtype with a tendency for atopic march early on in life may be good targeted candidates for anti-IgE drugs (25). However anti-IgE treatments in AD have shown largely negative results. Omalizumab is a recombinant humanized monoclonal IgG1κ antibody used in chronic spontaneous urticaria and asthma. Despite some case series demonstrating favorable efficacy for AD, omalizumab did not show improved efficacy over placebo in an RCT (103). A phase IV trial for severe pediatric AD was completed, but results have not yet been posted. In a phase II trial, patients treated with ligelizumab (QGE031), a high affinity anti-IgE Ab,

every 2 weeks for 12 weeks did not show a significant reduction in the severity for AD compared to placebo (104). The phase I trials using other anti-IgE agents, such as MEDI4212 (NCT01544348) and XmAb7195 (NCT02148744) have been completed, but show limited potential (105, 106). To date, anti-IgE approaches do not appear to have significant clinical activity in AD.

IL-1α antagonist

IL-1α, a prototypical pro-inflammatory cytokine, is an attractive target as its major reservoir appears to be keratinocytes, which may play a key role in the initiation of the inflammatory cascade found in AD (107). IL-1α also enhances matrix metalloproteinases activity, thereby leading to epithelial barrier breakdown (108). Bermekimab (MABp1) is a naturally derived human mAb that shows immunomodulating activity by blocking IL-1α activity. The drug failed in a phase III for colorectal cancer, but is now being evaluated for inflammatory skin diseases like hidradenitis suppurativa and AD. A phase II trial of 38 patients with moderate-to-severe AD revealed significant improvements at all clinical endpoints (109). Controlled studies are needed to better assess the potential of this novel therapy in AD.

JAK inhibitors

JAK inhibitors potentially have a wide application in inflammatory skin diseases including AD. JAK is a key mediator in signaling numerous cytokines involved in the pathogenesis of AD, including IL-4 and IL-13. Notably, IL-4 requires signaling through JAK1/3 while IL-13 signals through JAK1/TYK2 (110). The JAK-STAT pathway may play an important role in mediating both inflammation and pruritus in AD (40). Baricitinib is a potent oral JAK1/JAK2 inhibitor approved in the EU and the US for the treatment of rheumatoid arthritis. In a phase II trial, patients with moderate-to-severe AD showed significant improvements in EASI-50 at week 16, 61% (4mg) versus 37% (placebo) when treated with baricitinib in combination with TCS (111). Patients also reported tolerating the medication well with improvements in pruritus and sleep. Dose-dependent adverse events including headache, increased creatine phosphokinase, and nasopharyngitis were reported. Two phase III trials BREEZE-AD1 and BREEZE-AD2 confirmed significant clinical efficacy in both baricitinib doses of 2 mg and 4 mg with a good safety profile for patients with moderate-to-severe AD (112). A number of phase III trials for baricitinib that include combination therapy with TCS and longer-term endpoints are still being recruited. Upadacitinib (ABT-494), a selective oral JAK1 inhibitor, is currently underway in clinical trials for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis. In a phase IIb trial, upadacitinib showed reduction in pruritus as early as week 1 and a significant

dose-dependent improvement in EASI score at week 2 in patients with moderate-to-severe AD (113). Adverse events included URIs and AD exacerbations. Further phase III trials including younger patients with moderate-to-severe AD are also currently underway. In a phase IIb trial, abrocitinib (PF-04965842), a selective oral JAK1 inhibitor, showed dose-dependent improvement in EASI and IGA scores at week 12 versus placebo (40). The top-line results detailed in a press release of a phase III trial of abrocitinib showed statistically significant results with good tolerability and no unexpected safety events (114). Other phase III trials with long-term treatment periods are now being investigated. In a short-term clinical I trial (NCT03139981), ASN002 (Gusacitinib), a dual inhibitor of pan-JAK (JAK1-3, TYK2) and SYK, showed improvement in clinical severity at week 4 with a reduction in Th2/Th22 biomarkers (115). Another phase II trial with longer duration is still ongoing. Oral tofacitinib in a small open-label study showed impressive reductions in SCORAD with no adverse events (116).

PDE4 inhibitor

PDE4 inhibitor increases intracellular cAMP levels, leading to a down regulation of a number of cytokines involved in AD including IL-2, IL-5, IL-13 IL-17, IL-22, IL-31, and IL-33 (117). PDE inhibitor also upregulates the anti-inflammatory cytokine IL-10. Apremilast, an oral PDE4 inhibitor approved for psoriasis and psoriatic arthritis, showed promising results in an AD pilot study (118). However, in a phase II trial, apremilast showed no significant change in EASI score at week 12 at a dose of 30 mg compared to placebo. Although apremilast at a dose of 40 mg showed clinical efficacy and decreased Th17/Th22 related biomarkers, it was discontinued due to serious adverse event like cellulitis (119).

Chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes antagonists

Chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes (CRTH2) is a prostaglandin D2 receptor that is expressed on Th2 cells, eosinophils, and basophils. It stimulates the initiation of Th2 cell migration in the skin (120). Two PoC phase II trials for two CRTH2 antagonists, OC000459 (ODC-9101) and fevipiprant (QAW039) had been completed, but results did not demonstrate efficacy (121, 122).

Histamine receptor type 4 antagonists

Histamine (H) is a known itch-inducing mediator. Yet, the roles of H1 and H2 blockade in AD and AD-associated itching has been rather disappointing (123). Histamine receptor type 4 (H4R) is expressed on Th2 cells, Th17 cells, keratinocytes, and sensory neural cells. H4 stimulation also stimulates IL-31 production (124). JNJ-

39758979, an H4R antagonist, was terminated early in a phase IIa trial due to serious adverse events including agranulocytosis (NCT01497119) although it did show significant reduction in pruritus compared to placebo (125). In a phase II trial testing ZPL-389, another H4R antagonist, significant reductions in EASI and SCORAD scores were found at week 8 compared to placebo for patients with moderate-to-severe AD with concomitant use of TCS. However, there was no significant reduction in pruritus (126). Additional phase II trials of ZPL-389 are still ongoing.

Neuropeptide substance P and neurokinin 1 receptor antagonists

Neuropeptide substance P and neurokinin 1 receptor (NK1R), the receptor for substance P, is associated with AD disease activity (127). The NK1R antagonist prompts decreased scratching behavior in AD mouse models (128). In a PoC phase II trial for patients with AD and chronic pruritus, patients treated with oral tradipitant (VLY-686) for 4 weeks experienced a significant reduction in pruritus VAS from baseline ($p < 0.0001$) (129). A phase III trial for tradipitant is currently underway. In a phase II trial involving AD patients with severe pruritus, subjects taking oral serlopitant (VPD-737) for 6 weeks revealed numeric differences in pruritus scores compared to placebo. However, the differences were not statistically significant (130).

CONCLUSION

Despite its high prevalence worldwide, effective management of AD is complicated due to its multifaceted pathophysiology, variable clinical manifestations, and chronic course of the disease. The success of dupilumab in AD confirms the central importance of type 2 cytokines in the pathophysiology of AD. In addition to type 2 cytokines, certain phenotypes of AD may be driven by additional cytokine pathways. However, data to date attempting to specifically target cytokines outside of the type 2 axis have largely been unsuccessful. Broad acting JAK inhibition may help patients with AD that are driven by more complex cytokine endotypes. Further data using large-scale and longer-term clinical trials with proper outcome measures that assess signs, symptoms, quality-of life and long-term control as recommended by the HOME initiative (www.homeforeczema.org) are needed in order to create tailored and personalized treatments for AD. The results of studies for several other promising approaches targeting inflammation, the microbiome, itch, and PDE4 are eagerly awaited.

REFERENCES

1. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson E, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy 2018; 73: 1284–1293.
2. Otsuka A, Nomura T, Rerknimitr P, Seidel JA, Honda T, Kabashima K. The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis. Immunol Rev 2017; 278: 246–262.
3. Nakatsuji T, Gallo RL. The role of the skin microbiome in atopic dermatitis. Ann Allergy Asthma Immunol 2019; 122: 263–269.
4. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NM, et al. Patient burden of moderate to severe atopic dermatitis (AD): insights from a phase 2b clinical trial of dupilumab in adults. J Am Acad Dermatol 2016; 74: 491–498.
5. Patel KR, Immaneni S, Singam V, Rastogi S, Silverberg JI. Association between atopic dermatitis, depression, and suicidal ideation: A systematic review and meta-analysis. J Am Acad Dermatol 2019; 80: 402–410.
6. Czarnowicki T, Esaki H, Gonzalez J, Malajian D, Shemer A, Noda S, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)+ TH2/TH1 cell imbalance, whereas adults acquire CLA+ TH22/TC22 cell subsets. J Allergy Clin Immunol 2015; 136: 941–951. e943.
7. Grewe M, Bruijnzeel-Koomen CA, Schöpf E, Thepen T, Langeveld-Wildschut AG, Ruzicka T, et al. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. Immunol Today 1998; 19: 359–361.
8. Grewe M, Walther S, Gyufko K, Czech W, Schöpf E, Krutmann J. Analysis of the cytokine pattern expressed in situ in inhalant allergen patch test reactions of atopic dermatitis patients. J Invest Dermatol 1995; 105: 407–410.
9. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of TH2/TH22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012; 130: 1344–1354.
10. Werfel T, Allam J-P, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. J Allergy Clin Immunol 2016; 138: 336–349.
11. Malajian D, Guttman-Yassky E. New pathogenic and therapeutic paradigms in atopic dermatitis. Cytokine 2015; 73: 311–318.
12. Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. J Invest Dermatol 2008; 128: 2625–2630.
13. Czarnowicki T, Krueger JG, Guttman-Yassky E. Skin barrier and immune dysregulation in atopic dermatitis: an evolving story with important clinical implications. J Allergy Clin Immunol Pract 2014; 2: 371–379.
14. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nature Genet 2006; 38: 441.
15. Brandt EB, Sivaprasad U. Th2 cytokines and atopic dermatitis. J Clin Cell Immunol 2011; 2. pii: 110.
16. Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought? J Allergy Clin Immunol 2017; 140: 633–643.
17. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov 2016; 15: 35.
18. Danso MO, Van Drongelen V, Mulder A, Van Esch J, Scott H, Van Smeden J, et al. TNF-α and Th2 cytokines induce atopic dermatitis–like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. J Invest Dermatol 2014; 134: 1941–1950.
19. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell–mediated allergic inflammation by producing TSLP. Nature Immunol 2002; 3: 673.
20. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 2006; 117: 411–417.

21. Kim BS, Wojno EDT, Artis D. Innate lymphoid cells and allergic inflammation. Curr Opin Immunol 2013; 25: 738–744.
22. Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, Wang X, et al. A role for IL-25 and IL-33–driven type-2 innate lymphoid cells in atopic dermatitis. J Exp Med 2013; 210: 2939–2950.
23. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016; 387: 40–52.
24. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016; 375: 2335–2348.
25. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol 2019; 143: 1–11.
26. Kezic S, O'Regan GM, Lutter R, Jakasa I, Koster ES, Saunders S, et al. Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. J Allergy Clin Immunol 2012; 129: 1031–1039. e1031.
27. Esaki H, Brunner PM, Renert-Yuval Y, Czarnowicki T, Huynh T, Tran G, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. J Allergy Clin Immunol 2016; 138: 1639–1651.
28. Noda S, Suárez-Fariñas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. J Allergy Clin Immunol 2015; 136: 1254–1264.
29. Thijs JL, Strickland I, Bruijnzeel-Koomen CA, Nierkens S, Giovannone B, Csomor E, et al. Moving toward endotypes in atopic dermatitis: identification of patient clusters based on serum biomarker analysis. J Allergy Clin Immunol 2017; 140: 730–737.
30. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. BMC Pediatrics 2016; 16: 75.
31. Hanifin JM. Phosphodiesterase and immune dysfunction in atopic dermatitis. J Dermatol Sci 1990; 1: 1–6.
32. Baumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. Inflamm Allergy Drug Targets 2007; 6: 17–26.
33. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol 2016; 75: 494–503. e496.
34. Ahmed A, Solman L, Williams H. Magnitude of benefit for topical crisaborole in the treatment of atopic dermatitis in children and adults does not look promising: a critical appraisal. Br J Dermatol 2018; 178: 659–662.
35. Manriquez JJ, Villouta MF, Williams HC. Evidence-based dermatology: number needed to treat and its relation to other risk measures. J Am Acad Dermatol 2007; 56: 664–671.
36. Eichenfield LF, Call RS, Forsha DW, Fowler Jr J, Hebert AA, Spellman M, et al. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. J Am Acad Dermatol 2017; 77: 641–649. e645.
37. Hanifin JM, Ellis CN, Frieden IJ, Fölster-Holst R, Gold LFS, Secci A, et al. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): a phase-II randomized, double-blind, placebo-controlled study. J Am Acad Dermatol 2016; 75: 297–305.
38. Pernis AB, Rothman PB. JAK-STAT signaling in asthma. J Clin Invest 2002; 109: 1279–1283.
39. Cotter DG, Schairer D, Eichenfield L. Emerging therapies for atopic dermatitis: JAK inhibitors. J Am Acad Dermatol 2018; 78: S53–S62.
40. He H, Guttman-Yassky E. JAK inhibitors for atopic dermatitis: an update. Am J Clin Dermatol 2019; 20: 181–192.
41. Wu N-L, Huang D-Y, Tsou H-N, Lin Y-C, Lin W-W. Syk Mediates IL—17-Induced CCL20 Expression by Targeting Act1-Dependent K63-Linked Ubiquitination of TRAF6. J Invest Dermatol 2015; 135: 490–498.
42. Amano W, Nakajima S, Kunugi H, Numata Y, Kitoh A, Egawa G, et al. The Janus kinase inhibitor JTE-052 improves skin barrier function through suppressing signal transducer and activator of transcription 3 signaling. J Allergy Clin Immunol 2015; 136: 667–677. e667.
43. Bissonnette R, Papp K, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase II a randomized trial. Br J Dermatol 2016; 175: 902–911.
44. Nakagawa H, Nemoto O, Igarashi A, Nagata T. Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. Br J Dermatol 2018; 178: 424–432.
45. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. Cell 2017; 171: 217–228. e213.
46. Kim B. A Phase 2, Randomized, Dose-Ranging, Vehicle- and Active-Controlled Study to Evaluate the Safety and Efficacy of Topical Ruxolitinib in Adult Patients With Atopic Dermatitis (Abstract). 27th EADV congress, Paris, France, September 12–16, 2018.
47. Haarmann-Stemmann T, Esser C, Krutmann J. The Janus-faced role of aryl hydrocarbon receptor signaling in the skin: consequences for prevention and treatment of skin disorders. J Invest Dermatol 2015; 135: 2572–2576.
48. van den Bogaard EH, Bergboer JG, Vonk-Bergers M, van Vlijmen-Willems IM, Hato SV, van der Valk PG, et al. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. J Clin Invest 2013; 123: 917–927.
49. Kimura A, Naka T, Nohara K, Fujii-Kuriyama Y, Kishimoto T. Aryl hydrocarbon receptor regulates Stat1 activation and participates in the development of Th17 cells. Proc Natl Acad Sci U S A 2008; 105: 9721–9726.
50. Li J, Chen G, Wu H, Webster JM. Identification of two pigments and a hydroxystilbene antibiotic from Photorhabdus luminescens. Appl Environ Microbiol 1995; 61: 4329–4333.
51. Bissonnette R, Chen G, Bolduc C, Maari C, Lyle M, Tang L, et al. Efficacy and safety of topical WBI-1001 in the treatment of atopic dermatitis: results from a phase 2A, randomized, placebo-controlled clinical trial. Arch Dermatol 2010; 146: 446–449.
52. Bissonnette R, Poulin Y, Zhou Y, Tan J, Hong H, Webster J, et al. Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized, placebo-controlled double-blind trial. Br J Dermatol 2012; 166: 853–860.
53. Maeda-Chubachi T, Johnson L, Bullman J, Collingwood T, Bissonnette R. Tapinarof cream for atopic dermatitis: Pharmacokinetics, systemic exposure, and preliminary efficacy/safety results: 5243. J Am Acad Dermatol 2017; 76; AB247.
54. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res 2012; 22: 850–859.
55. Simpson EL, Villarreal M, Jepson B, Rafaels N, David G, Hanifin J, et al. Patients with atopic dermatitis colonized with Staphylococcus aureus have a distinct phenotype and endotype. J Invest Dermatol 2018; 138: 2224–2233.
56. Myles IA, Earland NJ, Anderson ED, Moore IN, Kieh MD, Williams KW, et al. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. JCI Insight 2018; 3. pii: 120608.
57. Nakatsuji T, Chen TH, Narala S, Chun KA, Two AM, Yun T, et al. Antimicrobials from human skin commensal bacteria protect against Staphylococcus aureus and are deficient in atopic dermatitis. Sci Transl Med 2017; 9: eaah4680.
58. Simpson EL, Bruin-Weller M, Flohr C, Ardern-Jones MR, Barbarot S, Deleuran M, et al. When does atopic dermatitis

warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. J Am Acad Dermatol 2017; 77: 623–633.

59. Kagami S, Saeki H, Komine M, Kakinuma T, Tsunemi Y, Nakamura K, et al. Interleukin-4 and interleukin-13 enhance CCL26 production in a human keratinocyte cell line, HaCaT cells. Clin Exp Immunol 2005; 141: 459–466.

60. Ungar B, Garcet S, Gonzalez J, Dhingra N, da Rosa JC, Shemer A, et al. An integrated model of atopic dermatitis biomarkers highlights the systemic nature of the disease. J Invest Dermatol 2017; 137: 603–613.

61. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 2013; 368: 2455–2466.

62. DUPIXENT® (dupilumab) Injection. Package insert. Regeneron Pharmaceuticals, Inc., Tarrytown, NY; Sanofi-Aventis U.S., Bridgewater, NJ; 2019.

63. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017; 389: 2287–2303.

64. de Bruin-Weller M, Thaçi D, Smith C, Reich K, Cork M, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol 2018; 178: 1083–1101.

65. Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol 2019; 143: 155–172.

66. Han Y, Chen Y, Liu X, Zhang J, Su H, Wen H, et al. Efficacy and safety of dupilumab for the treatment of adult atopic dermatitis: a meta-analysis of randomized clinical trials. J Allergy Clin Immunol 2017; 140: 888–891. e886.

67. Wang F-P, Tang X-J, Wei C-Q, Xu L-R, Mao H, Luo F-M. Dupilumab treatment in moderate-to-severe atopic dermatitis: a systematic review and meta-analysis. J Dermatol Sci 2018; 90: 190–198.

68. Wollenberg A, Ariens L, Thurau S, van Luijk C, Seegräber M, de Bruin-Weller M. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab–clinical characteristics and treatment. J Allergy Clin Immunol Pract 2018; 6: 1778–1780. e1771.

69. Eichenfield LF, Bieber T, Beck LA, Simpson EL, Thaçi D, de Bruin-Weller M, et al. Infections in Dupilumab Clinical Trials in Atopic Dermatitis: A Comprehensive Pooled Analysis. Am J Clin Immunol 2019; 20: 443–456.

70. Blauvelt A, Simpson EL, Tyring SK, Purcell LA, Shumel B, Petro CD, et al. Dupilumab does not affect correlates of vaccine-induced immunity: a randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. J Am Acad Dermatol 2019; 80: 158–167. e151.

71. Wollenberg A, Beck L, Blauvelt A, Simpson E, Chen Z, Chen Q, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). Br J Dermatol 2020; 182: 1120–1135.

72. Hamid Q, Naseer T, Minshall EM, Song YL, Boguniewicz M, Leung DY. In vivo expression of IL-12 and IL-13 in atopic dermatitis. J Allergy Clin Immunol 1996; 98: 225–231.

73. Esche C, de Benedetto A, Beck LA. Keratinocytes in atopic dermatitis: inflammatory signals. Curr Allergy Asthma Rep 2004; 4: 276–284.

74. Simpson EL, Flohr C, Eichenfield LF, Bieber T, Sofen H, Taïeb A, et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). J Am Acad Dermatol 2018; 78: 863–871. e811.

75. Press release [Internet]. California: Dermira Inc. 2019 [Mar 18]. Dermira Announces Positive Topline Results from Phase 2b Study of Lebrikizumab in patients with Atopic Dermatitis. Available from: https://investor.dermira.com/news-releases/default.aspx.

76. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, et al. Treatment of atopic dermatitis with tralokinumab, an anti–IL-13 mAb. J Allergy Clin Immunol 2019; 143: 135–141.

77. Nakajima S, Igyártó BZ, Honda T, Egawa G, Otsuka A, Hara-Chikuma M, et al. Langerhans cells are critical in epicutaneous sensitization with protein antigen via thymic stromal lymphopoietin receptor signaling. J Allergy Clin Immunol 2012; 129: 1048–1055. e1046.

78. Murakami-Satsutani N, Ito T, Nakanishi T, Inagaki N, Tanaka A, Vien PTX, et al. IL-33 promotes the induction and maintenance of Th2 immune responses by enhancing the function of OX40 ligand. Allergol Int 2014; 63: 443–455.

79. Wang Y-H, Ito T, Wang Y-H, Homey B, Watanabe N, Martin R, et al. Maintenance and polarization of human TH2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells. Immunity 2006; 24: 827–838.

80. Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, et al. Tezepelumab, an anti–thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. J Am Acad Dermatol 2019; 80: 1013–1021.

81. Guttman-Yassky E, Pavel AB, Zhou L, Estrada YD, Zhang N, Xu H, et al. GBR 830, an anti-OX40, improves skin gene signatures and clinical scores in patients with atopic dermatitis. J Allergy Clin Immunol 2019; 144: 482–493.e7.

82. Kyowa Kirin Inc. Product monograph. A phase I study of KHK4083 in subjects with atopic dermatitis. 2018 [Dec 8]. Available from: https://ir.kyowakirin.com/en/library/events/main/02/teaserItems1/0/linkList/00/link/181203_02_KHK4083_en.pdf.

83. Dillon SR, Sprecher C, Hammond A, Bilsborough J, Presnell SR, Haugen HS, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. Nature Immunol 2004; 5: 752.

84. Hamann CR, Thyssen JP. Monoclonal antibodies against interleukin 13 and interleukin 31RA in development for atopic dermatitis. J Am Acad Dermatol 2018; 78: S37–S42.

85. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, et al. Anti–interleukin-31 receptor A antibody for atopic dermatitis. N Engl J Med 2017; 376: 826–835.

86. Kabashima K, Furue M, Hanifin JM, Pulka G, Wollenberg A, Galus R, et al. Nemolizumab in patients with moderate-to-severe atopic dermatitis: Randomized, phase II, long-term extension study. J Allergy Clin Immunol 2018; 142: 1121–1130. e1127.

87. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz J-D, Wollenberg A, et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. J Allergy Clin Immunol 2020; 145: 173–182.

88. Mikhak Z. First-in-human study of KPL-716, anti-oncostatin M receptor beta monoclonal antibody, in healthy volunteers and subjects with atopic dermatitis (Abstract). 27th EADV congress, Paris, France, September 12–16, 2018.

89. Haldar P. Patient profiles and clinical utility of mepolizumab in severe eosinophilic asthma. Biologics 2017; 11: 81.

90. Oldhoff J, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 2005; 60: 693–696.

91. Peng W, Novak N. Recent developments in atopic dermatitis. Curr Opin Allergy Clin Immunol 2014; 14: 417–422.

92. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. J Am Acad Dermatol 2018; 78: 872–881. e876.

93. Brunner PM, Pavel AB, Khattri S, Leonard A, Malik K, Rose S, et al. Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. J

Allergy Clin Immunol 2019; 143: 142–154.

94. Hamilton JD, Suárez-Fariñas M, Dhingra N, Cardinale I, Li X, Kostic A, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol 2014; 134: 1293–1300.

95. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol 2017; 140: 645–653.

96. Ramirez-Carrozzi V, Sambandam A, Luis E, Lin Z, Jeet S, Lesch J, et al. IL-17C regulates the innate immune function of epithelial cells in an autocrine manner. Nature Immunol 2011; 12: 1159.

97. Shroff A, Guttman-Yassky E. Successful use of ustekinumab therapy in refractory severe atopic dermatitis. JAAD case reports 2015; 1: 25.

98. Puya R, Alvarez-López M, Velez A, Asuncion EC, Moreno JC. Treatment of severe refractory adult atopic dermatitis with ustekinumab. Int J Dermatol 2012; 51: 115–116.

99. Khattri S, Brunner PM, Garcet S, Finney R, Cohen SR, Oliva M, et al. Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. Exp Dermatol 2017; 26: 28–35.

100. Saeki H, Kabashima K, Tokura Y, Murata Y, Shiraishi A, Tamamura R, et al. Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. Br J Dermatol 2017; 177: 419–427.

101. Thaçi D, Constantin MM, Rojkovich B, Timmis H, Klöpfer P, Härtle S, et al. MOR106, an anti-IL-17C mAb, a potential new approach for treatment of moderate-to-severe atopic dermatitis: phase 1 study. Presented at: American Academy of Dermatology Annual Meeting; Feb 16-20, 2018; San Diego, CA, USA.

102. Novak N, Valenta R, Bohle B, Laffer S, Haberstok J, Kraft S, et al. FcεRI engagement of langerhans cell–like dendritic cells and inflammatory dendritic epidermal cell–like dendritic cells induces chemotactic signals and different T-cell phenotypes in vitro. J Allergy Clin Immunol 2004; 113: 949–957.

103. Bangert C, Loesche C, Jones J, Weiss D, Bieber T, Stingl G. Efficacy, safety and pharmacodynamics of a high-affinity anti-IgE antibody in patients with moderate to severe atopic dermatitis: a randomized, double-blind, placebo-controlled, proof-of-concept study. Experimental Dermatology: Wiley-Blackwell, Hoboken, USA, 2016: p. 37–37.

104. Novartis Clinical Trial No. CQGE031X2201. 2016 [Mar 15]. Available from: https://www.novctrd.com/CtrdWeb/displaypdf.nov?trialresultid=12404.

105. Sheldon E, Schwickart M, Li J, Kim K, Crouch S, Parveen S, et al. Pharmacokinetics, pharmacodynamics, and safety of MEDI4212, an anti-IgE monoclonal antibody, in subjects with atopy: a phase I study. Adv Therapy 2016; 33: 225–251.

106. Hu J, Chen J, Ye L, Cai Z, Sun J, Ji K. Anti-IgE therapy for IgE-mediated allergic diseases: from neutralizing IgE antibodies to eliminating IgE+ B cells. Clin Transl Allergy 2018; 8: 27.

107. Bou-Dargham MJ, Khamis ZI, Cognetta AB, Sang QXA. The role of interleukin-1 in inflammatory and malignant human skin diseases and the rationale for targeting interleukin-1 alpha. Med Res Rev 2017; 37: 180–216.

108. Han Y-P, Downey S, Garner WL. Interleukin-1α–induced proteolytic activation of metalloproteinase-9 by human skin. Surgery 2005; 138: 932–939.

109. Simpson E. Bermekimab is a Rapid and Effective Treatment for Atopic Dermatitis (Abstract). AAD annual meeting, Washington, DC, USA, March 1–5 2019.

110. Hershey GKK. IL-13 receptors and signaling pathways: an evolving web. J Allergy Clin Immunol 2003; 111: 677–690.

111. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol 2019; 80: 913–921. e919.

112. Simpson E. Efficacy and safety of baricitinib in moderate-to-severe atopic dermatitis: results of two phase 3 monotherapy randomized, double-blind, placebo-controlled 16-week trials (BREEZE-AD1 and BREEZE-AD2) (Abstract) 24th World Congress of Dermatology meeting, Milan, Italy, June 10–15, 2019.

113. Guttman-Yassky E. Primary Results from a Phase 2b, Randomized, Placebo-Controlled Trial of Upadacitinib for Patients with Atopic Dermatitis (Abstract). AAD annual meeting, San Diego, USA, February 16–20, 2018.

114. Press release [Internet]. New York: Pfizer Inc. 2019 [Oct 12]. Pfizer Presents Positive Phase 3 Data at the 28th Congress of the European Academy of Dermatology and Venereology for Abrocitinib in Moderate to Severe Atopic Dermatitis. Available from: https://www.pfizer.com/news/press-release.

115. Guttman-Yassky E, Pavel A, Song T, Kim H, Zammit D, Toker S, et al. 559 ASN002 a dual oral inhibitor of JAK/SYK signaling improves clinical outcomes and associated cutaneous inflammation in moderate-to-severe atopic dermatitis patients. J Invest Dermatol 2018; 138: S95.

116. Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. J Am Acad Dermatol 2015; 73: 395–399.

117. Gottlieb AB, Matheson RT, Menter A, Leonardi CL, Day RM, Hu C, et al. Efficacy, tolerability, and pharmacodynamics of apremilast in recalcitrant plaque psoriasis: a phase II open-label study. J Drugs Dermatol 2013; 12: 888–897.

118. Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. Arch Dermatol 2012; 148: 890–897.

119. Simpson EL, Imafuku S, Poulin Y, Ungar B, Zhou L, Malik K, et al. A phase 2 randomized trial of apremilast in patients with atopic dermatitis. J Invest Dermatol 2019; 139: 1063–1072.

120. Mitson-Salazar A, Yin Y, Wansley DL, Young M, Bolan H, Arceo S, et al. Hematopoietic prostaglandin D synthase defines a proeosinophilic pathogenic effector human TH2 cell subpopulation with enhanced function. J Allergy Clin Immunol 2016; 137: 907–918. e909.

121. https://www.clinicaltrials.gov/ct2/show/NCT02002208.

122. https://www.clinicaltrials.gov/ct2/show/NCT01785602.

123. Apfelbacher CJ vZE, Fedorowicz Z, Jupiter A, Matterne U, Weisshaar E. Oral H1 antihistamines as monotherapy for eczema. Cochrane Database Syst Rev 2013;(2):CD007770.

124. Gutzmer R, Mommert S, Gschwandtner M, Zwingmann K, Stark H, Werfel T. The histamine H4 receptor is functionally expressed on TH2 cells. J Allergy Clin Immunol 2009; 123: 619–625.

125. Murata Y, Song M, Kikuchi H, Hisamichi K, Xu XL, Greenspan A, et al. Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of a H4R-antagonist (JNJ-39758979) in Japanese adults with moderate atopic dermatitis. J Dermatol 2015; 42: 129–139.

126. Werfel T, Layton G, Yeadon M, Whitlock L, Osterloh I, Jimenez P, et al. Efficacy and safety of the histamine H4 receptor antagonist ZPL-3893787 in patients with atopic dermatitis. J Allergy Clin Immunol 2019; 143: 1830–1837. e1834.

127. Toyoda M, Nakamura M, Makino T, Hino T, Kagoura M, Morohashi M. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. Br J Dermatol 2002; 147: 71–79.

128. Ohmura T, Hayashi T, Satoh Y, Konomi A, Jung B, Satoh H. Involvement of substance P in scratching behaviour in an atopic dermatitis model. Eur J Pharmacol 2004; 491: 191–194.

129. PR Newswire [Internet]. Washington: Vanda Pharmaceuticals 2015 [Mar 4]. Vanda Pharmaceuticals Announces Tradipitant Phase II Proof of Concept Study Results for Chronic Pruritus in Atopic Dermatitis. [last accessed 2019 Sep 30]. Available from: https://www.prnewswire.com/news-releases/vanda-pharmaceuticals-announces-tradipitant-phase-ii-proof-of-concept-study-results-for-chronic-pruritus-in-atopic-dermatitis-300045700.html.

130. Ständer S, Spellman MC, Kwon P, Yosipovitch G. The NK1 receptor antagonist serlopitant for treatment of chronic pruritus. Expert Opin Investig Drugs 2019; 28: 659–666.