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Current and emerging biologic and small molecule therapies for atopic dermatitis

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Abbreviations:

AD: Atopic dermatitis

AMP: Adenosine monophosphate

cAMP: Cyclic adenosine monophosphate

CPK: Creatine phosphokinase

DC: Dendritic cell

DGLA: Dihomo- γ -linolenic acid

DPP-4: Dipeptidyl peptidase-4

EASI: Eczema Area and Severity Index

FLG: Filaggrin

H4R: Histamine H4 receptor

IHC: Immunohistochemistry

IVL: Involucrin

JAK-STAT: Janus kinase/signal transducers and activators of transcription

KOR: Kappa-opioid receptors

LOR: Loricrin

MOR: Mu-opioid receptors

NK-1R: Neurokinin-1 Receptor

NLRP3: NLR family, pyrin domain containing 3

OR: Opioid receptor

OSMR β : Oncostatin M receptor beta

PDE4: Phosphodiesterase 4

qRT-PCR: Quantitative real-time PCR

SCORAD: SCORing Atopic Dermatitis

SP: Substance P

SYK: Spleen tyrosine kinase

TCS: Topical corticosteroids

TCI: Topical calcineurin inhibitors

TSLP: Thymic stromal lymphopoietin

TYK2: Tyrosine kinase 2

Abstract:

Introduction: Atopic dermatitis (AD) is the most common inflammatory skin disease, yet until recently there were no safe systemic therapies approved for the long-term management of AD in adult patients. A deeper understanding of disease pathogenesis and identification of molecular and cellular changes has resulted in a rapidly evolving pipeline of therapeutics that holds promise for safer long-term control.

Areas Covered: In this review, we highlight the growing arsenal of biologic and small molecule antagonists that target pathways implicated in AD pathogenesis. Evidence that AD is driven by multiple immune axes extending beyond the Th2 polarization has resulted in therapies targeting additional pathways, including the Th22, Th17/IL-23, and JAK-STAT pathways. Pruritus, a hallmark of AD, has been

linked to multiple mechanisms and various therapeutics have emerged in response to alternative hypotheses.

Expert opinion: Despite the assumption that AD has a common disease mechanism, recent studies indicate that the disorder is characterized by several phenotypes and therapy may need to be tailored to the unique immune traits of specific phenotypes. Targeted therapy should complement and expand our molecular map of AD across the various phenotypic iterations and help push AD pharmacotherapy into a new era of personalized medicine.

Key words: Atopic dermatitis, Eczema; Therapeutics; Biologics; Monoclonal antibody; Small molecule; Targeted treatment



1. Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease, with increasing prevalence and 3%-10% of adults affected worldwide [1, 2, 3, 4]. AD is characterized by oozing, “wet” skin lesions in its acute stage and lichenified lesions in the chronic stage, although acute and chronic lesions typically coincide in AD patients [1, 2]. These lesions usually affect the face and flexors and are accompanied by prominent itch [2]. Up to one-third of individuals with AD have moderate-to-severe skin symptoms, and while a new monoclonal antibody, dupilumab, has been recently approved by the FDA

and other authorities, there still remains a large unmet need for effective and safe therapies for long-term disease control [5, 6]. Current guidelines for AD treatment include the use of moisturizers as a cornerstone for all levels of severity, with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) utilized for acute flares and maintenance therapy [7, 8]. However, it is estimated that about 10% of adult patients have AD that does not adequately respond to topical therapy [9]. In these cases, narrow-band UVB and systemic immunomodulatory agents such as cyclosporine A and methotrexate have been recommended [8, 10, 11]. However, potential serious adverse effects limit their long-term use [9]. Systemic corticosteroids can also be used to bridge therapy to alternative systemic treatment, but long-term use is strongly discouraged [12]. Thus, until recently there were no safe systemic therapies approved for the long-term management of AD in adult patients [13]. This changed in 2017 with the FDA approval of dupilumab, the first targeted systemic treatment for moderate-to-severe AD [14, 15, 16, 17, 18]. The effectiveness of dupilumab therapy has opened the door to testing of many other injectable and oral medications that will be discussed here.

The pathogenesis of AD combines epidermal-barrier dysfunction and immune activation with genetic predisposition and microbial dysbiosis [19, 20]. Traditionally, two competing hypotheses have been postulated behind the pathogenesis of AD. In the “inside-out” theory, an intrinsic defect in the immune system leads to barrier dysfunction, while the “outside-in” theory hypothesizes that permeability barrier dysfunction leads to penetration by pathogens and subsequent immune activation [21, 22]. In recent years,

the approach towards AD development has shifted away from this “chicken and egg” debate with the advent of genomics, transcriptomics, and proteomics technology [23]. Molecular profiling has allowed for greater understanding of disease pathogenesis and identification of skin and blood changes that can precede clinical alterations [24, 25, 26, 27]. Similar to psoriasis, tissue and blood profiling assist to define pathogenic pathways and treatment response biomarkers [28, 29].

While psoriasis is centered on one axis alone, the Th17/IL-23 pathway [30, 31], AD is a more complex inflammatory disease with Th2 and Th22 polarization, some contributions from Th17/IL-23 and Th1 axes, and additional microbiome and environmental interactions [1, 2, 20, 32]. Importantly, biomarker-based studies indicate that there are different AD subpopulations with distinct molecular and cellular characteristics [33, 34, 35]. While all the AD phenotypes share common Th2 activation, there are important differences between these disease subtypes, necessitating varying treatment approaches [33, 34, 35, 36, 37, 38, 39]. In this review, we will review the mechanisms, efficacy, and safety of biologic and small molecule antagonists that compose the rapidly evolving pipeline for AD pharmacotherapy.

2. Biologics

2.1. Th2 Inhibition Strategies

2.1.1. Anti-IL-4/IL-13

AD has historically been associated with a Th2-mediated immune response and overexpression of IL-4, IL-5, IL-13, IL-31, and other Th2 related cytokines [1, 40]. The contributions of IL-4/IL-13 to the AD pathogenesis are multi-factorial. IL-4/IL-13 have been shown to disrupt the integrity of the skin barrier through the downregulation of structural proteins including loricrin (LOR), filaggrin (FLG), and involucrin (IVL) [41, 42]. Production of chemokines such as CCL26 is strongly enhanced by IL-4/IL-13, driving the migration of eosinophils in a Th2 immune response [43]. IL-4/IL-13 also have a twofold impact on skin colonization by *Staphylococcus aureus*. These cytokines inhibit the formation of antimicrobial peptides and allow for entry by bacteria, while simultaneously augmenting the effects of α -toxin mediated cytotoxicity and keratinocyte cell death [44, 45].

Interestingly, it has also been shown that IL-13 alone can cause an inflammatory skin response similar to AD [46]. IL-13 upregulates thymic stromal lymphopoietin (TSLP), a cytokine produced in the epidermis that directs dendritic cells toward a Th2 response. It also stimulates tissue remodeling and mucus hypersecretion [47]. A study to examine the relative importance of IL-4 and IL-13 in AD revealed that IL-13 mRNA was significantly upregulated relative to IL-4 mRNA, suggesting that IL-13 may be the crucial cytokine in lesional AD skin [48].

Dupilumab is a fully human monoclonal antibody against the α chain of the IL-4 receptor (IL-4R α), which is a receptor for both IL-4 and IL-13. It is the first biologic therapy and monoclonal antibody developed and approved for moderate-to-severe AD in adult patients in the USA and EU [49]. Since 2012, a total of eight randomized, double-blinded placebo-controlled controlled trials (including three phase III trials) have demonstrated the efficacy of dupilumab across various clinical indexes at improving the signs and symptoms of moderate-to-severe AD in adult patients [17, 18, 50, 51]. Ligand binding to the IL-4R α receptor modulates gene expression in the Th2 pathway [52]. Dupilumab-treated patients demonstrated a reduction in traditional molecular markers in AD such as genes associated with Th2 inflammation (IL-13, IL-31, CCL17, CCL18, CCL26) [14, 16, 18]. Gene analysis also revealed a decrease in mRNA expression of epidermal hyperplasia-related genes (K16, MKi67) and an increase in expression of epidermal differentiation and barrier genes (FLG, LOR, claudins) [14, 16, 18]. Furthermore, reductions in expression of Th17/Th22-modulated genes such as PI3/Elafin, IL23p19/IL23A, and S100 proteins have been demonstrated, suggesting that the Th17 pathway may be linked to IL-4 signaling [16]. While dupilumab is well tolerated, clinical trials of dupilumab have reported an increased incidence of conjunctivitis that correlates with more severe baseline AD that responds well to the drug [17, 53]. The relationship between conjunctivitis and dupilumab remains unclear. A phase III study (NCT02612454) is underway to assess the safety and efficacy of dupilumab in children greater than six months and less than eighteen years of age, but recently reported data show significant efficacy in adolescents [54].

Lebrikizumab and tralokinumab are monoclonal antibodies that target the IL-13 cytokine. Although dupilumab has been shown to reduce symptoms of AD by inhibiting both IL-4 and IL-13, the overlap of their signaling pathways and biologic structure have led to the hypothesis that blockade of IL-13 alone might lead to a more specific method of action [48]. IL-13 initiates its signaling pathway through binding the heterodimeric receptor consisting of IL-13R α 1 and IL-4R α [55]. Although both lebrikizumab and tralokinumab bind to soluble IL-13 with strong affinity, lebrikizumab blocks the ability of IL-13 to bind to the IL-4R α portion of the receptor, while tralokinumab blocks the ability of IL-13 to bind to the IL-13R α 1 and IL-13R α 2 subunits [56].

A phase II study demonstrated the percentage of patients achieving EASI-50 was significantly greater ($P < 0.05$) for lebrikizumab (82%) compared to placebo (62%), with concomitant use of topical corticosteroids [57]. Notably, the final weeks of the study continued to show an upward sloping response curve, suggesting that a longer treatment duration might lead to increased efficacy rates. A dose-response relationship was observed and may suggest that further increases in dose could improve efficacy. These results signify that future studies with variable dosing and duration, and without topical steroids, may better clarify the role of targeting IL-13 with lebrikizumab in AD. Lebrikizumab was well tolerated with no increase in adverse effects when compared to placebo. A modest increase in blood eosinophil counts has been observed [58]. This is most likely due to blocking of IL-13 induced chemokines and adhesion molecules that

can serve as chemoattractants for eosinophils, resulting in their accumulation in blood [57, 58]. An additional monotherapy phase II study (NCT03443024) for lebrikizumab is ongoing.

Similarly, a phase II study that also included concomitant topical corticosteroids determined that tralokinumab was associated with significant improvement ($P < 0.05$) in AD symptoms based upon EASI score and IGA score over a twelve-week period [59]. Of note, dipeptidyl peptidase-4 (DPP-4) and periostin are considered biomarkers for IL-13 and mRNA expression of both have been shown to be induced by IL-13 [60, 61]. DPP-4 is induced in bronchial epithelial cells by IL-13 and has been associated with eosinophilic airway inflammation [62]. Periostin is an extracellular matrix protein that recruits eosinophils during Th2 mucosal inflammation [63]. An exploratory analysis on tralokinumab was also done during the same phase II study where patients with increased DPP-4 and periostin concentrations were evaluated for improvement [59]. Participants in these subgroups displayed greater reductions in serum biomarker concentrations and additional improvements in EASI scores compared to participants with normal levels of DPP-4 and periostin. These results indicate that DPP-4 and periostin may have value as predictors of treatment response. Common adverse events related to tralokinumab treatment were upper respiratory tract infection and headache [59, 64]. A phase III trial (NCT03363854) is being conducted on the efficacy and safety of tralokinumab.

2.1.2. Anti-IL-31

IL-31 is primarily produced by Th2 cells and may play a significant role in the induction of pruritus in AD [65, 66, 67]. Significantly increased IL-31 expression ($P < 0.05$) was observed in inflammatory infiltrates from skin biopsies taken from subjects with AD compared to healthy controls [1, 67, 68, 69, 70]. Administration of IL-31 in mice has been shown to trigger a skin phenotype that resembles AD [66]. Importantly, a study on NC/Nga mice demonstrated treatment with anti-IL-31 antibody resulted in reduced scratching behavior and could be a potential therapeutic approach for pruritus in AD [71]. IL-31 signals through a heterodimeric receptor composed of the interleukin 31 receptor alpha (IL-31RA) and oncostatin M receptor (OSMR), directly activating primary afferent neurons in the skin [67, 72]. Consequently, IL-31RA is the critical neuroimmune link between Th2 cells and sensory nerves for the generation of T cell mediated itch [67].

IL-31 also has additional roles in AD pathogenesis beyond pruritus. Keratinocytes express IL-31RA and activation by IL-31 results in cell cycle arrest, reduced expression of filaggrin, and reduced epidermal thickness [73]. Stimulation of keratinocytes by IL-31 also causes the release of chemokines that recruit lymphocytes and monocytes to the epidermis [66]. In addition, eosinophils express IL-31RA and secrete proinflammatory cytokines and chemokines upon IL-31 stimulation [74]. The activation of keratinocytes and eosinophils indicate that IL-31 is part of a broader proinflammatory response.

Nemolizumab is a humanized antibody against IL-31RA. A phase II trial that allowed application of topical corticosteroids after 4 weeks found a significant, dose-dependent reduction ($P < 0.01$) in pruritus scores from baseline for nemolizumab (~60%) compared to placebo (~21%) [75]. Nemolizumab groups also demonstrated decreases in EASI score and SCORAD score, which were particularly significant for the 0.5mg/kg dose. A 52-week extension of the phase II trial showed that improvements in pruritus compared to placebo were either maintained or further increased with long-term treatment [76]. The most common adverse events were nasopharyngitis, upper respiratory infection, and peripheral edema. An additional monotherapy phase II study (NCT03100344) for nemolizumab is underway.

2.1.3. Anti-OSMR β

The oncostatin M receptor beta protein (OSMR β) is a subunit of both the type II oncostatin M receptor (OSMR) and IL-31RA [77, 78]. The type II OSMR is expressed on epidermal keratinocytes and is upregulated in AD [77]. Interaction between type II OSMR and oncostatin M (OSM), a member of the IL-6 family that is primarily secreted by T cells, induces a Th2 inflammatory response, alters epidermal integrity, and generates fibrotic change [77, 78, 79, 80, 81, 82, 83, 84, 85, 86]. Activation of type II OSMR leads to a proinflammatory response characterized by an increased production of Th2 cytokines (IL-4 and IL-13) and chemokines (eotaxin-1/2, MCP-1) [82]. OSMR

stimulation has also been shown to compromise the epidermal barrier through the induction of S100 proteins and suppression of other epidermal differentiation markers such as LOR, FLG, and IVL [83]. In addition, OSMR activation causes extracellular matrix accumulation and fibrosis through regulation of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs), promotion of fibroblast proliferation, and direct induction of type I collagen [82, 85]. Synergies between OSM and IL-4/IL-13 further heighten Th2 inflammation, while synergies between OSM and IL-17A add to the fibrotic response [84]. As mentioned previously, activation of the IL-31RA receptor can induce pruritus and Th2 inflammation.

KPL-716 is an anti-OSMR β monoclonal Ab that inhibits both IL-31 and OSM signaling through binding a single epitope [87]. A double-blind, placebo-controlled phase 1a/1b clinical trial of KPL-716 demonstrated a -42.3% decrease in EASI, compared to a -25.0% decrease in placebo recipients at day 28 [88]. Furthermore, patients in the KPL-716 arm experienced a decrease of -40.4% in mean percentage change for weekly-average Worst-Itch Numeric Rating Scale (WI-NRS) and a -55.4% decrease for Pruritus Visual Analog Scale (VAS) compared to -17.6% decrease for WI-NRS and a -10.4% decrease for VAS in the placebo arm [88]. KPL-716 was well tolerated with only mild dizziness, headache, and decreased appetite reported [88].

2.1.4. Anti-OX40

TSLP is expressed primarily in keratinocytes and is considered a “master switch” of allergic inflammation at the epithelial cell-DC interface [89]. Following insults from allergens, TSLP is released by keratinocytes and serves to activate immature DCs and increase their expression of OX40L [90]. Through OX40L, TSLP-stimulated DCs directly stimulate the differentiation of naïve CD4⁺ T cells into a unique subset of inflammatory memory Th2 cells. While OX40L is expressed on DCs that are termed “atopic DCs,” OX40 is also expressed by activated T cells and memory T cells after antigen exposure and the OX40-OX40L interaction is critical as a late signal for long-term CD4 T cell survival by promoting the expression of antiapoptotic proteins Bcl-xL and Bcl-2 [91, 92, 93]. Two studies studying the pathway upstream of the OX40-OX40L interaction lend further credence to its important role in the pathogenesis of AD. First, transgenic mice that overexpressed the TSLP transgene exhibited an AD-like phenotype with a concomitant increase in Th2 cells [94]. Second, ablation of the retinoid X receptors in keratinocytes led to an AD-like phenotype that was accompanied by a strong overproduction of TSLP by keratinocytes before any other Th2 cytokine [95].

GBR 830 is a monoclonal IgG antibody against OX40 currently in a phase IIb clinical trial (NCT03568162). The results of the phase IIa trial showed significant reductions from baseline in hyperplasia measures ($P < 0.001$) and AD biomarkers ($P < 0.01$) such as Th2 cytokines and Th17/Th22-associated products [96]. The percentage of patients achieving EASI-50 was greater, but not significantly different between GBR 830 (44%) compared to placebo (20%), with significant reductions in some biomarkers; the drug

was well-tolerated [96]. Another fully human monoclonal antibody against OX40, KWK4083, completed a preliminary phase IIa trial in Japan with encouraging results and continuous reductions in EASI scores and TARC levels until week 22, after only 3 IV doses [97]. Tezepelumab, a TSLP antagonist, failed to demonstrate clinical efficacy in a phase IIa trial (NCT02525094), while a clinical trial for the TSLPR antagonist MK-8226 were prematurely halted due to business reasons (NCT01732510).

2.1.5. Anti-IL-33

IL-33 is a cytokine secreted by epithelial cells in response to damage, exposure to allergens, or colonization by *Staphylococcus aureus* [98, 99]. IL-33 plays a key role in Th2 immune response and has been shown to stimulate Th2 cells to release IL-4, IL-5, and IL-13 in mice [100]. IL-33 also enhances the OX40L-driven differentiation of naïve Th2 cells and increases production of IL-5, IL-9, and IL-13 [101]. Furthermore, IL-33 leads to increased IgE levels, inhibits the expression of filaggrin, and activates a wide range of cells involved in inflammatory processes [100, 102, 103]. High levels of IL-33 and ST2, an IL-33-specific receptor, have been observed in lesional AD skin, as well as in food-patch-tested skin [25, 26, 99, 104]. A study utilizing an anti-IL-33 antibody in AD-induced mice showed an improvement in symptoms and a significant reduction in eosinophils, mast cells, and serum IgE [105].

Etokimab is a monoclonal IgG antibody against IL-33 [106]. A phase IIa trial with twelve patients demonstrated encouraging results with all participants experiencing at least EASI-50 response before Day 57 and improvement in SCORAD and IGA scores [107]. The most common adverse effect was headache, but the drug was otherwise well-tolerated. A phase IIb trial (NCT03533751) for patients with moderate-to-severe AD has been initiated.

2.2. Th22 Inhibition Strategies

2.2.1. Anti-IL-22

Although AD has been classically described as a Th2-centered disease, Th22 T-cells that secrete IL-22 also play a crucial role in pathogenesis of AD [28, 29, 108, 109, 110]. IL-22 CD8⁺ T-cells have been found to correlate with AD disease severity and analysis of AD lesions revealed significantly elevated levels of genes ($P < 0.005$) associated with the Th22 pathway, including IL-22, IL-32, S100A7, S100A8, and S100A9 [1, 108]. IL-22 signals through a receptor composed of two chains, the IL-22RA1 subunit and the IL-10RB chain [111]. Activation of the receptor leads to epidermal hyperplasia, keratinocyte migration, down-regulation of keratinocyte differentiation genes such as FLG and LOR, and increased expression of S100 proinflammatory molecules [112, 113, 114]. Consequently, the continual rise of levels of IL-22 in chronic AD lesions compared to acute AD lesions may explain the psoriasis like hyperplastic epidermis in the chronic

phase of AD [108, 115]. The Th22 pathway may also have complex interplay with other aspects of AD pathogenesis. The disrupted epithelial barrier caused by IL-22 may lead to TSLP-stimulated DC activation of the hallmark Th2 pathway [20]. It has also been shown that Staphylococcal enterotoxin B and α -toxin induce IL-22 production in peripheral blood mononuclear cells and could explain how *S. aureus* contributes to skin inflammation in AD [116].

Fezakinumab is a monoclonal IgG antibody against IL-22 [117]. A phase IIa trial demonstrated significant declines ($P < 0.05$) in SCORAD at week 12 for a severe AD subset of patients, but only numerical declines in SCORAD during the same period for all AD patients [117]. Analysis of the AD genomic profile with fezakinumab treatment demonstrated significant suppression of mRNA expression of multiple genes related to the Th1, Th17, and Th22 pathways for patients with high IL-22 baseline expression, representing one of the first approaches towards precision medicine for patients with AD [118]. Fezakinumab showed a favorable safety profile with upper respiratory tract infections being the most common adverse event [117]. Patients with insufficient response to dupilumab may benefit from fezakinumab due to its targeting of an alternative pathway.

2.3. Th17/IL-23 Inhibition Strategies

2.3.1. Anti-IL-12/23p40

Psoriasis is a Th17/IL-23-skewed inflammatory skin disease whose pathogenesis has been confirmed by successful, targeted treatment [30]. In contrast, AD has classically been considered Th2/Th22-skewed. This view has been challenged with recent studies showing elevated levels of Th17/IL-23 cytokines and products in AD patients, including IL-17A, IL-23, CCL20, and PI3/Elafin [1]. Although all AD phenotypes share Th2 activation, it has been shown that AD is a heterogeneous disorder with certain phenotypes (Asian AD, intrinsic AD, pediatric AD) displaying enhanced IL-17 expression that might warrant more targeted therapy [33, 34, 35].

Th17 cells have been shown to enhance and potentially induce the development of AD [119, 120]. This is supported by the correlation of AD severity with the percentage of Th17 cells in peripheral blood of AD patients and with some IL-17-induced markers in serum [24, 27, 119]. IL-23 released from inflammatory myeloid DCs causes the differentiation of naïve T cells into Th17 cells and induces epidermal hyperplasia driven by the downstream production of IL-22 and IL-17A [121, 122]. IL-17A has also been implicated in the Th2 differentiation of naïve T cells in AD [120]. Th17 cells are more markedly expressed in acute lesions compared to chronic lesions, which may highlight their role as an initial proinflammatory cytokine source for the development of skin lesions [123].

Ustekinumab is an IgG monoclonal antibody that binds the p40 subunit of heterodimer cytokines IL-12 and IL-23. IL-12 drives differentiation of CD4⁺ T cells towards the Th1 phenotype, while IL-23 induces Th17 differentiation [124]. In this way, ustekinumab inhibits both the Th1 and Th17 pathways. Ustekinumab has been shown to be effective in reducing inflammation in psoriasis and the potential role of the Th17 pathway in AD led to a phase II study investigating the safety and efficacy of ustekinumab in patients with moderate-to-severe AD [124]. Ustekinumab produced greater SCORAD-50 responses compared to placebo, but the differences were not significant [125]. Improvements in genes related to Th1, Th17, and Th2 AD pathways were observed and showed the strongest anti-inflammatory effects between 4-8 weeks, with waning efficacy thereafter.

Secukinumab is an IgG1 antibody to IL-17A that has also shown effective results in psoriasis therapy [31]. A phase II clinical trial (NCT02594098) is underway and seeks to compare efficacy between sets of groups that may differ in Th17 polarization, including intrinsic and extrinsic AD patients, Asian and non-Asian AD patients, and patients who exhibit higher baseline levels of IL-17A and IL-17F.

2.4. IL-17C Inhibition Strategies

2.4.1. Anti-IL-17C

IL-17C is distinct from IL-17A and other classical T-cell cytokines due to its exclusive production by epithelial cells, its autocrine method of action on keratinocytes through binding to the receptor IL-17RA-IL-17RE complex, and the lack of association with the Th17 pathway [126]. It acts as a local amplifier of skin inflammation, with reported synergistic loops with IL-1 and IL-22 [126, 127]. IL-17C stimulates the expression of proinflammatory cytokines, chemokines, and antimicrobial peptides involved in tissue remodeling and has been recently reported to be increased in AD lesions [127].

MOR106 is an IgG1 monoclonal antibody that binds IL-17C and inhibits its interaction with the IL-17RE receptor. A phase I study showed reductions in Th2-related products such as IL-4, IL-33, TSLP, and CCL17, while also achieving reductions in Th17/Th22-related products like IL-17A, IL-22, S100A8, S100A9m and LCN2 [127]. In addition, 83% of patients achieved EASI-50 by week 4 in the highest dose group compared to less than 20% in the placebo group [128]. A phase II study is underway (NCT03568071).

2.5. IgE Inhibition Strategies

2.5.1. Anti-IgE

AD is associated with elevated serum IgE levels and it has been shown that these levels are correlated with clinical severity [129]. IgE allows for processing of allergens by dendritic cells and subsequent presentation to Th2 cells [130, 131]. In addition, IgE mediates mast cell activation and the release of histamine and other cytokines that promote Th2 polarization [130, 131].

Omalizumab is a recombinant monoclonal antibody that targets IgE. A systematic review and meta-analysis of thirteen studies showed that less than half of patients receiving omalizumab for AD achieved marked clinical improvement and there was no evidence of overall effectiveness in adults [132]. A study analyzing biomarkers of patient subgroups that may respond to omalizumab revealed that responders are characterized by absence of filaggrin mutations and altered lipid metabolite profiles [133]. A study is currently looking into the role of anti-IgE treatment in severe childhood eczema (NCT02300701).

3. Small Molecule Antagonists

3.1. JAK Inhibitors

The JAK-STAT pathway is a signal transduction pathway for cytokines and growth factors that has been shown to be a common denominator for many of the processes

implicated in the pathogenesis of AD [134]. The JAKs include a group of 4 receptor-associated kinases: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) [135]. After binding to their specific ligand, non-receptor tyrosine kinases activate and result in JAK mediated intracellular phosphorylation of STATs, which translocate to the cell nucleus to regulate target genes [135, 136].

In AD, allergens penetrate the skin and are detected by DCs, which initiate Th2 differentiation through TSLP receptor activation of STAT1, STAT3, STAT5/JAK1, and JAK2 [90, 137]. Development of Th2 cells is also initiated by IL-4 and IL-13 differentiation signals that utilize JAK1/3 and JAK1/2, respectively [138]. Signals via the STAT-6 pathway also allow IL-4 and IL-13 to down-regulate barrier proteins FLG, LOR, and IVL [41, 139]. In addition, the JAK-STAT pathway is responsible for the differentiation of Th17 cells through STAT3 mediated IL-23 and IL-6 pathways [140]. Finally, IL-31 may cause pruritus in AD patients through STAT3 mediated β -endorphin production in keratinocytes [141]. Since AD is a disease involving activation of several immune pathways, JAK inhibitors may be effective in AD patients as they target more than one cytokine pathway [142]. There are currently four oral JAK inhibitors under investigation for AD: baricitinib, PF-04965842, upadacitinib, and ASN002.

Baricitinib is a selective oral inhibitor of JAK1 and JAK2 [142, 143]. JAK1 has been associated with modulation of cytokines in acute lesions in AD (IL-4, IL-6, IL-10, IL-13,

IL-31, and IFN- γ) [121, 144, 145]. JAK2 has been associated with modulation of cytokines in both acute lesions (IL-5, IL-6, IL-23, IL-31, IFN- γ , GM-CSF) and chronic lesions (IL-23) [121, 144]. A phase II study demonstrated significant improvement ($P < 0.05$) in EASI scores for baricitinib (65%) compared to placebo (46%) for moderate-to-severe AD patients [143]. Baricitinib was well tolerated, although a trend of elevated creatine phosphokinase (CPK) was observed with no associated symptoms [143]. A phase III study is ongoing (NCT03334396).

Upadacitinib and PF-04965842 are selective oral inhibitors of JAK1. Phase II studies of both JAK inhibitors have demonstrated clinically significant results, with significant improvement ($P < 0.05$) in EASI scores for upadacitinib (74%) compared to placebo (23%) and IGA scores for PF-04965842 (45%) compared with placebo (6%) [146, 147]. The most common adverse events for upadacitinib were upper respiratory tract infection, and acne [147]. A case of eczema herpeticum and pneumonia were recognized and deemed treatment related for PF-04965842 during the clinical trial [146]. Phase III studies for both upadacitinib (NCT03569293) and PF-04965842 (NCT03349060) are underway.

ASN002 is a dual oral JAK/SYK inhibitor that seeks to target epidermal differentiation and multiple cytokines across the Th2, Th22, Th1, and Th17 axes. Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase that plays a key role in terminal

differentiation of keratinocytes [148]. SYK controls the activation of the NLR family, pyrin domain containing 3 (NLRP3) inflammasome [149]. In response to foreign pathogens and tissue damage, NLRP3 activation leads to IL-1 β processing and release [149]. IL-1 β has been shown to promote upregulation of the Th17 pathway which, as previously discussed, can potentiate the development of AD. In a phase Ib clinical trial, significant clinical improvements in EASI scores were shown compared to placebo [150]. Dose-dependent reductions in serum AD biomarkers were also observed, including general inflammation, epidermal hyperplasia, Th2, Th22, and Th1 measures. The most common side effect was headache, mostly restricted to day 1 of treatment. A phase II study is ongoing (NCT03531957).

3.2. Phosphodiesterase 4 Inhibitor

Phosphodiesterase 4 (PDE4) is an intracellular enzyme responsible for the degradation of cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP) [151]. PDE4 is found in T cells and macrophages, and mediates the levels of proinflammatory molecules, including Th2 inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13 [152, 153, 154]. Through inhibiting PDE4, levels of cAMP increase and activate protein kinase A (PKA), which can phosphorylate proteins involved in cytokine synthesis such as NF- κ B and CREB [155, 156].

Apremilast is an orally available PDE4 inhibitor that has been approved for the treatment of psoriasis [157]. A phase II, placebo-controlled trial of apremilast 40 mg

BID (NCT02087943) in moderate to severe AD patients demonstrated significant improvements in EASI with a -31.6% decrease from baseline compared to -11.0% for placebo [158]. Patients who received apremilast 30 mg BID only showed a trend towards greater EASI improvement vs. placebo and did not reach statistical significance [158]. Notable adverse effects included cellulitis, which only occurred in the apremilast 40 mg BID arm, leading to the discontinuation of this dose at the recommendation of a data safety monitoring board [158].

3.3. Histamine H4 Receptor Antagonist

Four types of histamine receptors have been identified and recent studies highlighted the role of histamine H4 receptor (H4R) in inflammatory processes. AD patients have shown higher levels of H4R mRNA in keratinocytes compared to healthy patients [159]. H4R is expressed on Th2 T-cells and is upregulated by IL-4 [160]. Stimulation of H4R on Th2 cells leads to upregulation of IL-31, potentially contributing to pruritus in AD [160]. Also, stimulation of H4R on keratinocytes leads to epidermal hyperplasia observed in patients with AD [159]. Studies on mice have found that H4R antagonism in tandem with H1R antagonism leads to a decrease in signature AD cytokines, a reduction in IgE levels, and improvement in clinical scores [161]. A phase II study of a H4R-antagonist in Japanese adults with moderate AD displayed numerical improvements in EASI scores before being stopped early due to neutropenia [162].

ZPL-389 is a selective H4R antagonist. Significant improvement ($P = 0.01$) was shown for EASI scores in ZLP-389 (50%) compared to placebo (27%) in a phase II trial [163]. Surprisingly, the effect on pruritus was similar between ZPL-389 and placebo groups. ZPL-389 was well tolerated with no serious adverse events. A second phase II clinical trial is underway (NCT03517566).

3.4. Neurokinin-1 Receptor Antagonist

The tachykinin Substance P (SP) is a potent neuropeptide that may contribute to pruritus in AD through mast cell degranulation of histamine upon SP interaction with the Neurokinin-1 Receptor (NK-1R) [164, 165]. It has been shown that plasma SP levels correlate with AD activity and may be a useful biomarker [166]. Application of a NK-1R antagonist in NC/Nga mice significantly inhibited scratching behavior [167].

Two NK-1R antagonists (tradipitant and serlopitant) for AD recently completed phase II clinical trials with conflicting results. Significant improvement ($P < 0.05$) in measurement of itch was demonstrated for tradipitant compared to placebo [168]. Consistent with improvements with itch, significant improvement ($P < 0.01$) was also shown in total SCORAD for tradipitant compared to placebo [168]. Conversely, a press release announced differences between serlopitant and placebo did not reach statistical significance [169]. Both drugs were well tolerated with minimal side effects. A phase III clinical trial for tradipitant has been initiated (NCT03568331).

3.5. Kappa-Opioid Receptor Agonist

Opioid receptors (ORs) are G protein-coupled receptors located in the skin and central nervous system (CNS) [170]. Although three major classes of ORs exist, it is believed that the balance between mu- and kappa-opioid receptor systems determines the modulation of pruritus in the CNS [171]. Mu-opioid receptors (MOR) and kappa-opioid receptors (KOR) have been shown to have opposing effects in animal studies, with MOR playing a role in the induction of itch and KOR playing a role in the inhibition of itch [172]. Analysis of the epidermis of AD patients revealed the downregulation of KOR expression in AD patients compared to healthy volunteers with no difference in MOR expression [173].

Asimadoline is a selective oral KOR agonist that was found to reduce pruritus during preclinical studies for treatment of irritable bowel syndrome [174]. A phase II clinical trial showed significant improvement ($P < 0.05$) compared to placebo in both itching as measured by nighttime visual analogue scores and EASI scores [175]. The safety profile for asimadoline was mild.

4. Other Therapies

4.1. DGLA

It is hypothesized that AD may be a disorder of polyunsaturated fatty acid metabolism [176, 177, 178]. AD patients have demonstrated significantly lower levels of Dihomo- γ -linolenic acid (DGLA), an essential fatty acid, compared to healthy patients [179]. Via COX-1 and COX-2 pathways, DGLA is metabolized into anti-inflammatory eicosanoids [177, 180]. Specifically, the prostaglandin PGD₁ may prevent AD development through downregulating TSLP mRNA expression, suppressing mast cell and keratinocyte activation, and reducing itch [180]. DGLA may have antibacterial properties and has been shown to inhibit the growth of *Staphylococcus aureus* [181]. Oral administration of DGLA has been found to prevent the development of AD in NC/Nga mice and reduce clinical severity scores [180].

DS107 is an oral agent that contains > 95% pure DGLA as an active ingredient. A phase II trial demonstrated a trend toward a statistically significant proportion of patients who achieved an IGA score of 0 or 1 and a 2 point drop for DS107 (22%) compared to placebo (12%) [182]. No severe adverse events were noted, although more than one-quarter of subjects discontinued participation because of GI symptoms. A second phase II study is underway (NCT02864498) since the initial phase II trial's sample size was deemed too small to determine statistical significance.

5. Conclusion

The past decade has seen a transformational change in our understanding of the pathogenesis of atopic dermatitis [70, 183, 184]. Delineation of relevant immunologic axes has produced therapeutic fruit with the groundbreaking development of dupilumab, the first FDA-approved systemic treatment for AD since corticosteroids. Yet, the evolution of AD pharmacotherapy has only just begun. Multiple clinical trials for biologic and small molecule therapies in the AD pipeline have reached phase II and III status and hold promise towards furthering our understanding of what increasingly appears to be a complex, multifactorial disorder. Distinct and nuanced molecular data may provide an effective lens in which to develop targeted therapeutics as dermatology moves towards a bio-marker based system of personalized medicine. Ultimately, the goal of attaining effective and safe long-term options for the management of atopic dermatitis may be realistically attained in the near future.

6. Expert Opinion

The success of a translational-medicine model based on cellular and molecular analysis in psoriasis has sparked a similar approach for AD in the pursuit for more effective and safe therapeutics [29]. However, AD has presented additional challenges given that immune polarization differences between various AD subtypes may necessitate different therapeutic targeting [28]. The Th2 axis is commonly upregulated in all AD phenotypes, as demonstrated by the success of dupilumab. Yet, there are still many patients that do not resolve their AD in full with dupilumab as only ~1/3 of treated

patients achieved EASI-90 [50], highlighting the ongoing need for additional treatments tailored to the different AD subsets.

Part of our incomplete understanding of AD pathogenesis may be due to lack of diversity in clinical trials across ethnic groups, disease severity, and age groups. For example, clinical trials between 2000-2009 were predominantly conducted on individuals of European ancestry with 62% of patients identifying as White, despite other studies demonstrating AD disproportionately affects Black and Asian populations [34, 36, 185]. Recent data has suggested that pathogenic epidermal and immune elements in ethnic AD subsets may differ from those of European ancestry. AD has increasingly been identified as a group of heterogeneous phenotypes that vary along clinical manifestations and immune dysregulation. We advocate for future clinical trials to include analyses of subsets of patients representing different AD phenotypes. This will provide an increased understanding of differential treatment responses that will ultimately lead to the development of specific treatments for the various AD subcategories. Stratification for potential pathogenic immune differences between various AD clinical phenotypes may better account for these differences and hold the key for achieving a similar degree of success seen in psoriasis therapeutics. Indeed, we have shown that psoriasis and AD may actually exist on a spectrum with Asian AD, pediatric AD, and intrinsic AD demonstrating activation of the Th17/IL-23 pathway and a mixed phenotype that reflects features of psoriasis [33, 34, 35]. Despite the general assumption that AD has a common disease mechanism, these preliminary studies

seem to indicate that there are multiple disease endotypes and that targeted AD treatments may potentially show increased efficacy when tailored to the unique immune traits of specific phenotypes.

When classifying distinct phenotypes, challenges remain in measuring relative contributions from genetic predisposition, immune pathways, environmental factors, and microbiome contribution. Molecular profiling represents a significant step towards objective evaluation of baseline AD traits and therapeutic response. Furthermore, our research supports the hypothesis that severe AD may be best described as a systemic disease that extends to non-lesional skin and circulating biomarkers [27].

Understanding the alterations in both blood and tissue biomarkers that correlate with systemic dysfunction should be an area of great interest for future research and targeted therapy. As clinical trials in the AD pipeline advance, the growing arsenal of biologics and small molecule antagonists against different aspects of the involved immune pathways will complement and expand our molecular map of AD across its various phenotypic iterations and help push AD pharmacotherapy into a new era of personalized therapy.

Article highlights box:

- The success of immune pathway mapping in the treatment of psoriasis and the approval of dupilumab, the first biologic treatment for AD, have set the stage for a revolution in AD pharmacotherapy.

- Although traditionally considered a Th2 polarized skin disease, the increasing recognition of contributions from Th22, Th17/IL-23, and Th1 pathways have resulted in many exciting, targeted therapeutics that have reached phase II and III status and have shown encouraging early results.
- Addressing pruritus, a hallmark of AD, continues to be a priority in AD treatment and has led to the development of several promising therapeutics with disparate strategies, including a KOR agonist and antagonists of IL-31, NK-1R, and H4R.
- Success in clinical trials has commensurately contributed to a rapidly evolving understanding of the pathogenesis of AD and the emergence of a new paradigm of AD that has revealed the disorder to be a set of heterogeneous phenotypes.
- Unique contributions from immunologic pathways underlying specific AD phenotypes may justify the use of targeted therapies tailored to individuals.

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Papers of special note have been highlighted as either of interest (▪) or of considerable interest (▪▪) to readers.

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Table 1. Current and upcoming biologic and small molecule therapeutics for atopic dermatitis

	Agent	Target	Phase	Clinical Trial
Biologics	Dupilumab (Dupixent)	IL-4/IL-13	Approved, 2017; III for children	NCT02612454
	Lebrikizumab	IL-13	II	NCT03443024
	Tralokinumab	IL-13	III	NCT03363854
	Nemolizumab	IL-31RA	II	NCT03100344
	KPL-716	OSMR β	I	Not available
	GBR 830	OX40	II	NCT03568162
	KHK4083	OX40	I	NCT03096223
	Tezepelumab	TSLP	II completed	NCT02525094
	MK-8226	TSLPR	I completed	NCT01732510
	Etokimab (ANB020)	IL-33	II	NCT03533751
	Fezakinumab	IL-22	II completed	NCT01941537
	Ustekinumab (Stelara)	IL-12/23p40	II completed	NCT01806662
	Secukinumab (Cosentyx)	IL-17A	II	NCT02594098
	MOR106	IL-17C	II	NCT03568071
	Omalizumab	IgE	IV for children	NCT02300701
Small Molecule	Baricitinib	JAK 1/2	III	NCT03334396
	PF-04965842	JAK 1	III	NCT03349060
	Upadacitinib	JAK 1	III	NCT03569293
	ASN002	JAK/SYK	II	NCT03531957
	Apremilast	PDE4	II completed	NCT02087943
	Tradipitant	NK-1R	III	NCT03568331
	Serlopitant	NK-1R	II completed	NCT02975206
	ZPL-389	H4R	II	NCT03517566
Other	Asimadoline	KOR	II	NCT02475447
	DS107	DGLA	II	NCT02864498

Figure 1



Figure 1

Current and upcoming small molecules for atopic dermatitis

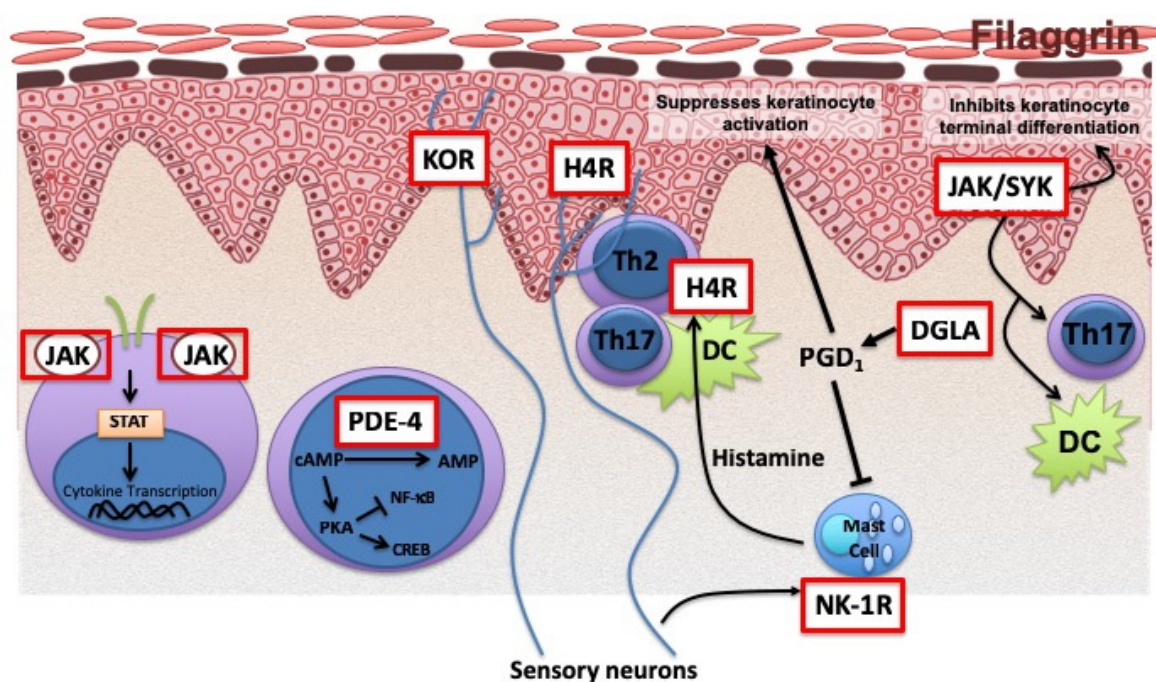


Figure 2