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REVIEW

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Understanding the immune landscape in atopic dermatitis: The era of biologics and emerging therapeutic approaches

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Abstract

Atopic dermatitis (AD) is a chronic, systemic, inflammatory disease that affects the skin and is characterized by persistent itch and marked redness. AD is associated with an increased risk of skin infections and a reduced quality of life. Most AD treatment options to date were not designed to selectively target disease-causing pathways that have been established for this indication. Topical therapies have limited efficacy in moderate-to-severe disease, and systemic agents such as corticosteroids and immunosuppressants present with tolerability issues. Advances in the understanding of AD pathobiology have made possible a new generation of more disease-specific AD therapies. AD is characterized by the inappropriate activation of type 2 T helper (Th2) cells and type 2 innate lymphoid (ILC2) cells, with a predominant increase in type 2 cytokines in the skin, including interleukin (IL)-13 and IL-4. Both cytokines are implicated in tissue inflammation and epidermal barrier dysfunction, and monoclonal antibodies targeting each of these interleukins or their receptors are in clinical development in AD. In March 2017, dupilumab, a human anti–IL-4Rα antibody, became the first biologic to receive approval in the United States for the treatment of moderate-to-severe AD. The anti–IL-13 monoclonal antibodies lebrikizumab and tralokinumab, which bind different IL-13 epitopes with potentially different effects, are currently in advanced-stage trials. Here, we briefly review the underlying pathobiology of AD, the scientific basis for current AD targets, and summarize current clinical studies of these agents, including new research to develop both predictive and response biomarkers to further advance AD therapy in the era of precision medicine.

KEYWORDS

atopic dermatitis, dupilumab, interleukin 13, interleukin 4, lebrikizumab, tralokinumab

1 | INTRODUCTION

Atopic dermatitis (AD), the most common inflammatory skin disease, is characterized by chronic, systemic inflammation, early age of onset, persistent itch, marked redness, cracking and/or dryness of the skin, and a relapsing course.[1–3] Prevalence of AD in the United States ranges from approximately 5% to 10% in adults and 10% to 13% in children, with moderate-to-severe disease occurring in about half of the adults (mean 54% [range 42%-73%]) and a third of the children (33%).[2,4–20] Moderate-to-severe AD is viewed as a systemic disease with increases in T and B cells in the circulation as well as in skin tissue.[21–26] The systemic nature of the disease is also

Matthew Moyle: Independent participation.

reflected in associated comorbidities, including cardiovascular, neuropsychiatric and malignant diseases, among others.[24,26–32]

Patients with AD often suffer from significantly reduced quality of life, with impairments in both social and physical functioning.[3] Patients with AD report occupational impairments, reduced productivity at school and work, interpersonal problems (eg social isolation, relationship issues) and reduced self-esteem.[33,34] For many, severe chronic itch impacts sleep and productivity.[34] Mental health disorders, including anxiety, depression and attention-deficit/hyperactivity disorder, are also more common in both children and adults with AD.[35,36] In addition, altered immune responses render patients with AD at increased risk of bacterial, viral and fungal skin infections, particularly by *Staphylococcus aureus* and herpes simplex type 1 virus.[29–31,37,38]

Conventional treatment approaches for AD, which include topical therapies (eg emollients, corticosteroids, calcineurin inhibitors), phototherapy and systemic agents, highlight the unmet need for safe and more durable therapies.[39–41] The Food and Drug Administration (FDA) has approved three topical treatments for AD, including pimecrolimus and tacrolimus (topical calcineurin inhibitors), and crisaborole ointment (topical phosphodiesterase-4 inhibitor). Although topical therapies are commonly used in treating mild disease, a number of disadvantages have been recognized: they do not address systemic inflammation, patients often relapse, and the therapies have limited efficacy in moderate-to-severe disease, where the affected body surface area is much greater.[42] While systemic therapies, including corticosteroids and immunosuppressants (eg cyclosporine A, methotrexate, azathioprine), have demonstrated efficacy, their long-term use is limited by poor adverse event and/or tolerability profiles.[33,42] Perhaps most important, conventional treatments are not specific in their targeting of the underlying disease biology.[40,41]

TABLE 1 Key characteristics of AD: Acute and chronic disease, non-lesional and lesional skin

Characteristic	Acute disease[a]	Chronic disease[b]
Type 2 pathway activation and related cytokines/chemokines	Increased (IL-4, IL-13, IL-31)[28,44,69,75,110–112]	Intensified (IL-5, IL-13, IL-31, IL-10, CCL5, CCL13, CCL18); mixed results for IL-4[28,33,44,69,75,110–112]
Type 22 pathway activation and related cytokines	Increased (IL-22)[28,44]	Intensified (IL-22, IL-32)[28,44]
Type 1 pathway activation and related cytokines/chemokines	Slightly increased (IFN-γ, MX1, IL-1β, CXCL9-11), but not in all phenotypes[32,44,51,113,114]	Significantly increased[44]
Type 17 pathway activation and related cytokines	Slightly increased (IL-17, IL-23p19, IL-23p40)[44]	Magnitude of activation is similar to that observed in acute disease[44]
Immune cell infiltration	Increased (T cells, ILC2s, DCs [mature and IDECs] and other myeloid cells)[44,115,116]	Intensified[44]
Epidermal changes	Increased hyperplasia, thickness and proliferation markers (Ki67, K16) as well as the IL-22–regulated S100A7-9 and S100A12 that mark epidermal hyperplasia;[44] reduced epidermal barrier proteins (involucrin, loricrin, filaggrin)[44]	Intensified[44]
Reduced expression of terminal differentiation proteins and lipids	Reduced expression of FLG, LOR, PPL and other differentiation proteins and significant lipid aberrations[44,61–63]	Intensified[44]
Characteristic	**Non-Lesional skin**	**Lesional skin**
Inflammatory cytokine and chemokine profile	Type 2 cytokines (IL-13, CCL18, CCL22), MX1, IL-22 and S100A7[28,47]	MMP12, type 2 cytokines (IL-13, CCL11, CCL17, CCL18, CCL22), type 1 cytokines (IFN-γ, CXCL10), IL-22, type 17 cytokines (IL-23p19, IL-12/23p40, CXCL1), PI3/elafin and S100 cytokine family members[28,47]
Immune cell infiltration	Increased (T cells, DCs [mature and IDECs] and other myeloid cells)[28,47,117]	Intensified[28,47]
Epidermal changes	Increased hyperplasia, thickness and epidermal proliferation markers (Ki67, K16), expression of S100As[28,47]	Intensified[28,47]
Expression of terminal differentiation markers	Downregulated and inversely correlated with disease severity (*IVL*, *LOR*, *PPL*, *FLG*)[28]	Magnitude of change is similar to that observed in non-lesional skin[28]

AD, atopic dermatitis; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; DC, dendritic cell; FLG, filaggrin; IDEC, inflammatory dendritic epidermal cell; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; IVL, involucrin; K16, keratin 16; LOR, loricrin; MMP, matrix metalloproteinase; PPL, periplakin.

[a]Acute lesions compared with non-lesional skin.

[b]Chronic lesions compared with acute lesions; "intensified," as it relates to changes, indicates substantial differences that are not always statistically significant.

TABLE 2 Key similarities and differences between IL-4 and IL-13

Characteristic	IL-4	IL-13
Expression in AD lesions	Mixed results for patient lesions[75,110]	Increased in acute and chronic patient lesions[69,75,110,112]
Signalling	Both type 1 and type 2 heterodimeric receptors: (1) IL-4Rα and γc and (2) IL-4Rα and IL-13Rα1[67,118]	Type 2 heterodimeric receptor only: IL-4Rα and IL-13Rα1[67,118]
Th2 cell differentiation	Stimulate and promote development[67,118]	Stimulate and promote development[118]
Tissue inflammation	Deficiency protects against AD in mouse model[68]	Expression associated with chronic inflammatory phenotype in mouse model[69]
Produced by cells	$CD4^+$ and $CD8^+$ T cells, mast cells, basophils, eosinophils[118–122]	$CD4^+$ and $CD8^+$ T cells, ILCs, mast cells, basophils, eosinophils, iNKTs[122–126]
IgE production	Activates B cells, augments antibody production and regulates IgE class switching[33]	
Epidermal barrier dysfunction	Promote keratinocyte damage and reduce filaggrin, loricrin and involucrin expression[33,70]	
Tissue fibrosis	No major role[67]	Promotes fibrotic skin remodelling[67,72]
Characteristics of detection	IL-4 protein and mRNA are rarely detected	IL-13 is commonly detected (eg in circulation, IL-13–positive T cells)
Murine models	Transgenic overexpression of IL-4[111] or IL-13[69] in epidermis of mice results in AD-like phenotype	

AD, atopic dermatitis; IgE, immunoglobulin E; IL, interleukin; IL-4Rα, IL-4 receptor alpha; IL-13Rα1, IL-13 receptor alpha 1; ILC, innate lymphoid cell; iNKT, invariant natural killer cell; mRNA, messenger ribonucleic acid; Th2, T helper cell type 2; γc, common gamma chain.

Improved understanding of AD disease pathophysiology has facilitated development of targeted therapeutic approaches that block disease-specific cytokines or receptors using antibodies. These disease-focused treatment approaches have demonstrated efficacy while also improving safety, leading to the potential for long-term care. One of these, dupilumab, has been approved in the United States for the treatment of adults (March 2017) and adolescents (March 2019) with moderate-to-severe AD. This review summarizes key AD pathophysiologic mechanisms and describes emerging therapeutic agents, with emphasis on biologics and the potential benefits they may bring to the clinic.

2 | AD PATHOPHYSIOLOGY: COMPLEX DYSREGULATION OF IMMUNE PATHWAYS

2.1 | The aberrant immune landscape and biomarkers of disease

Advances in the understanding of AD pathophysiology have demonstrated the role of systemic inflammation and immune dysfunction in mediating disease. Generally, the clinical presentation of acute and chronic eczematous skin lesions, respectively, differs in colour (bright versus dull red), thickness (flatter versus thicker) and spongiosis (marked versus minimal) of the dermis.[2,43,44] AD is characterized by aberrant and excessive Th2 cell and ILC2 activation, with robust expression of type 2 cytokines, including interleukin (IL)-4, IL-5, IL-13 and IL-31 (Table 1).[45–48] While activation of a type 2 immune response is common to all patients with AD, variable activation of other cytokines (particularly IL-22, but also IL-17, IL-9 and IFN-γ) is additionally seen, contributing to the diversity of clinical AD subtypes.[49–53] Analyses of transcriptomes from intra-individual acute and chronic skin lesions, as well as non-lesional skin from adult AD patients, indicate progressive changes in type 2 and type 22 (eg IL-22) pathway activation from acute to chronic disease, with induction of type 1 cytokine responses (eg IFN-γ) only in chronic lesions.[44] Studies in paediatric AD also showed a pattern of excessive type 2 inflammation, but with higher activation of type 9 and type 17 effectors at disease initiation.[51]

In acute AD lesions, the disease is characterized by significant increases in type 2 (eg IL-4, IL-13, IL-31)- and type 22-specific cytokines and corresponding downstream effects (Tables **1** and 2).[44,47] As key type 2 pathway mediators, IL-4 and IL-13 have multifaceted implications in AD pathophysiology, including propagation of inflammation, epidermal barrier dysfunction and itch.[33,42] Serum levels of IL-13 positively correlate with levels of the itch-promoting cytokine IL-31, which in turn have been correlated with disease severity.[54–57] Of note, IL-22 and the type 17-specific cytokine, IL-17, upregulate expression of certain S100 epidermal differentiation proteins including S100A7, S100A8 and S100A9.[58] These S100 proteins, along with IL-31 and IL-22, showed significant upregulation between non-lesional skin and acute lesions, with further increases in chronic lesions.[44] In chronic lesions, type 2- and type 22-specific inflammation is generally intensified compared with acute lesions, as indicated by increased expression of corresponding cytokines (eg IL-13 and IL-31 [type 2], IL-22 [type 22]).[44] Data are mixed for gene expression changes of IL-4 in chronic lesions, with some reports of decreased expression[44] and others reporting an increase.[33]

It is well established that epidermal barrier disruption contributes to AD pathophysiology, and marked skin changes are associated with lesion development (Table **1**).[59,60] Epidermal thickness and proliferation, assessed via keratin 16 (K16) and Ki67 expression, are increased in acute AD compared with non-lesional skin; these changes are significantly increased further in chronic versus acute AD lesions.[44] Terminal markers of epidermal differentiation,

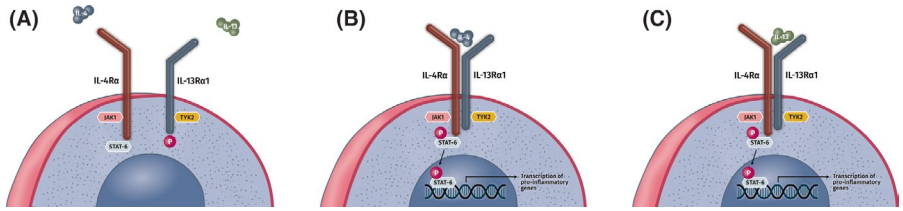

FIGURE 1 Type 2 receptor for IL-4 and IL-13. (A) The interleukin-4 type 2 receptor complex, comprised of IL-4Rα and IL-13Rα1 subunits. (B) Binding of IL-4 to IL-4Rα induces receptor dimerization with IL-13Ra1 and signal transduction via the JAK/STAT pathway, leading to increased transcription of genes associated with inflammation. (C) In a similar way, binding of IL-13 to IL-13Rα1 also induces dimerization with IL-4Ra, signal transduction and increased pro-inflammatory gene expression. IL, interleukin; IL-4Rα, IL-4 receptor alpha; IL-13Rα, IL-13 receptor alpha

including loricrin, periplakin and filaggrin, as well as tight junctions and lipids, are suppressed in chronic versus acute AD.[47,61–65] Lastly, immune cell infiltrates, including T cells, DCs (including mature and inflammatory dendritic epidermal cells [IDECs]) and myeloid cells, are significantly increased in acute versus non-lesional skin, with yet greater increases in chronic lesions.[44]

Transcriptomic and histologic profiling of lesional and non-lesional AD skin has elucidated differences in the inflammatory skin phenotypes that exist in AD (Table **1**).[28,47] Generally, changes observed in lesional skin are also present but less marked in non-lesional skin. Both are characterized by cellular and molecular abnormalities, including markers of epidermal hyperplasia, cellular infiltrates and increased inflammatory mediators compared with skin from individuals without AD.[27,28] The inflammatory changes evident in non-lesional skin may reflect, in part, the systemic nature of AD.[21,23–25,27,45]

While AD chronicity can further be characterized by a number of biomarkers identified in skin (eg IL-4, IL-13, IL-31, epidermal thickness),[44,47] a panel of serum biomarkers has also been shown to be increased in moderate-to-severe AD patients compared with healthy controls, speaking not only to the diagnostic utility of this approach, but also to the systemic nature of AD.[3,24,32,45,66] Given the intrusive nature of skin biopsies, serum inflammatory biomarkers may be a more practical alternative to assess severity, particularly in paediatric patients.[45]

2.2 | IL-4 and IL-13: Key type 2 immune mediators

2.2.1 | Receptors and downstream signalling molecules

While multiple molecules have been implicated in AD, studies in mice and humans have elucidated a central role for IL-4 and IL-13 (Table **2**).[33] IL-4– and IL-13–mediated signalling occurs via a shared heterodimeric receptor that comprises IL-13Rα1 and IL-4Rα, also known as the type 2 IL-4 receptor, which is expressed on most cell types (Figure 1).[33,67] Cytokine-mediated heterodimerization of the receptor subunits triggers subsequent downstream signalling via JAK1-mediated phosphorylation of the transcription factor STAT6, resulting in an overlap in function of IL-4 and IL-13, which has been well described in the literature.[33,67] IL-4 also signals through the type 1 IL-4 receptor that is made up of IL-4Rα and the common gamma chain, which is expressed chiefly on haematopoietic cells (eg T cells and B cells).

2.2.2 | Biological responses to IL-4 and IL-13

Both IL-4 and IL-13 stimulate immunoglobulin E (IgE) production from plasma cells, B-cell and plasma cell differentiation, and Th2 cell development/differentiation, among other effects (Table **2**).[33] They have both been implicated in tissue inflammation in mouse models of AD.[68,69] Additionally, both contribute to epidermal barrier dysfunction and keratinocyte damage in AD. Keratinocytes cultured in vitro in the presence of IL-4 and IL-13 had significantly reduced filaggrin expression irrespective of filaggrin mutation status.[70] Accordingly, filaggrin expression is significantly reduced in acute AD lesions compared with normal skin.[70] In addition to filaggrin, loricrin and involucrin are important for formation and integrity of the epidermal barrier,[33] and IL-4 and IL-13 downregulated loricrin and involucrin at the gene and protein level in primary keratinocytes.[71] Type 2 pathway activation can also trigger tissue fibrosis in AD through recruitment of fibrocytes to inflamed skin lesions.[72] IL-13–mediated tissue inflammation promotes fibrotic skin remodelling through the recruitment of fibroblasts and subsequent deposition of collagen.[72] Type 2 cytokines also directly induce activation of sensory neurons in murine models and in human dorsal root ganglia, eliciting chronic itch.[73,74]

Given the pleiotropic role of IL-4 and IL-13 in AD pathophysiology, several therapeutic approaches aimed at inhibiting these cytokines have been explored; these are described in detail in the next section. While gene expression studies in AD patients have suggested that IL-13 may be of greater pathophysiological importance,[75] ongoing and future clinical trials will help differentiate which of these two cytokines plays a more central role in this disease.

3 | THE ERA OF BIOLOGICS AND EMERGING THERAPEUTIC APPROACHES

Topical therapies have improved AD in mild cases but are not effective in patients with more severe disease, and may be difficult

to apply for patients with large amounts of affected body surface area.[42] While systemic immunosuppressants (eg corticosteroids, cyclosporine A, methotrexate) have demonstrated efficacy, they cannot be used long term due to poor tolerability.[42] For example, common side effects of corticosteroids include glucose intolerance, headaches and depression; those of cyclosporin A include headaches, nephrotoxicity and hypertension; and those of methotrexate are anaemia, leukopenia and hepatotoxicity.[33] Of these therapies, none are FDA-approved for the treatment of AD, though cyclosporine A is approved in Europe. Increased understanding of AD immunopathology has sparked development of targeted therapeutic approaches, and biologics have become a focus of research for AD treatments.

3.1 | Targeting IL-4 and IL-13

Given the multifaceted and central role of IL-4 and IL-13 in AD pathophysiology, a number of biologics targeting either IL-13 or both IL-4 and IL-13 pathways are under development (Figure 2). The essential role of the type 2 axis was validated by the clinical success of dupilumab, a fully human, IgG4κ monoclonal antibody targeting IL-4Rα and the first biologic approved for AD.[76–78] By antagonizing IL-4Rα, dupilumab blocks both IL-4– and IL-13–mediated signalling through the type 2 receptor, which requires heterodimerization of IL-4Rα and IL-13Rα1. Dupilumab also inhibits IL-4 signalling via the type 1 receptor.

Two IL-13–targeting antibodies, tralokinumab and lebrikizumab, are the most advanced IL-13–specific biologics in clinical development for the treatment of AD (Figure 1). Tralokinumab, an IgG4λ anti–IL-13 monoclonal antibody derived from a human phage display library, prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2.[79] The latter receptor has a short cytoplasmic tail and no known signalling motifs, and is thought to have an anti-inflammatory, decoy function via internalization of excess IL-13.[80,81] In this way, tralokinumab prevents both IL-13-mediated signalling downstream of IL-4Rα/IL-13Rα1 heterodimerization (type 2 receptor), but it may also interfere with endogenous regulation of IL-13 that is mediated by IL-13Rα2. Loss of function of the IL-13 decoy receptor was shown to be deleterious in a mouse model of cutaneous inflammation.[86] Lebrikizumab is a humanized, IgG4κ monoclonal antibody that also binds soluble IL-13 with high affinity, but at a different epitope compared with tralokinumab.[82] Lebrikizumab-bound IL-13 can still bind to its cell surface receptors, but the biologic prevents IL-4Rα/IL-13Rα1 heterodimerization (type 2 receptor) and downstream signalling. It does not, however, prevent IL-13 binding to the IL-13Rα2 decoy receptor. Although direct comparison of the biological differences between tralokinumab and lebrikizumab with respect to IL-13 modulation has not been done to date, a mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model was generated to understand the IL-13 profiles of two other anti-human IL-13 monoclonal antibodies evaluated in separate phase 1 trials (ie IMA-638 [NCT00339872; mild-to-moderate asthma] and IMA-026 [NCT00517348; healthy subjects]).[83] The two antibodies interfere with IL-13–mediated signalling by different mechanisms. IMA-638 prevents access of the prebound IL-13/IL-13Rα1 complex to the receptor signalling subunit IL-4Rα, while IMA-026 interferes with IL-13 binding to IL-13Rα1. Moreover, IMA-026 blocks binding of IL-13 to IL-13Rα2 and IMA-638 does not, so these antibodies may be considered surrogates for tralokinumab and lebrikizumab, respectively. While the PK profiles of IMA-638 and IMA-026 were similar, the total IL-13 (free- and drug-bound) profiles differed; specifically, the significant dose-dependent accumulation of total IL-13 observed with IMA-026 treatment was not evident following treatment with IMA-638. This finding suggests that prevention of IL-13 binding to the decoy receptor may result in heightened levels of systemic IL-13. The PK/PD model also predicted greater and more sustained inhibition of IL-13 with IMA-638 compared with IMA-026 when administered at equivalent doses. Although caution should be exercised when comparing IMA-026 and IMA-638 with tralokinumab and lebrikizumab, respectively, this study highlights differences in the IL-13 inhibitory potential between these similar antibodies with slightly different mechanisms of action. Further preclinical and mechanism of action data for tralokinumab and lebrikizumab are warranted to clearly dissect biological differences.

All three of these biologics (ie dupilumab, lebrikizumab and tralokinumab) have been evaluated in monotherapy and/or combination therapy studies in moderate-to-severe AD (tralokinumab, combination therapy only). Differences in study design (most notably trial duration, population size, whether topical corticosteroid (TCS) run-in was allowed and the dosing frequencies used) limit the ability to make direct comparisons among findings (Table **3**).[76–78,84,85] Importantly, a systematic review of published preclinical and clinical studies between January 2006 and October 2016 demonstrated no increase in the risk of serious safety signals (eg infection, malignancy, cardiovascular events) with anti–IL-13 alone or in combination with IL-4 via inhibition of IL-4Rα.[86] While long-term safety studies are necessary, these therapies generally appear to be safe and effective for the treatment of moderate-to-severe AD.[33,87] The relative clinical utility and potential individual advantages among these biologics remain to be determined, as their differences with respect to specific mechanistic targets, bioavailability, half-life and dosing frequency (among other attributes) have the potential to impact clinical experience.

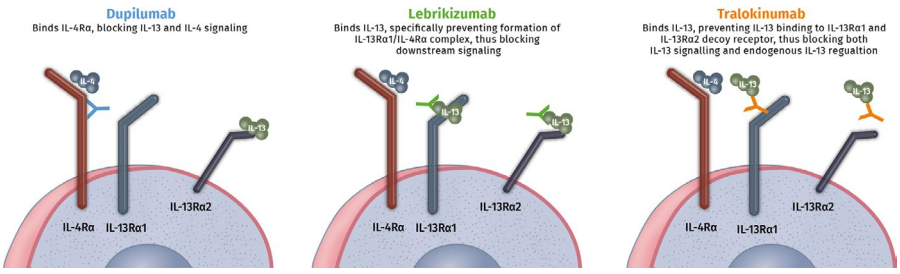

FIGURE 2 Mechanism of action for biologics targeting the IL-4 and/or IL-13 pathways. IL, interleukin; IL-4Rα, IL-4 receptor alpha; IL-13Rα, IL-13 receptor alpha

TABLE 3 Clinical trial design for completed trials of biologics targeting IL-4 and IL-13

	Dupilumab	Lebrikizumab	Tralokinumab
Clinical development status for M/S AD	Approved in the United States for adults and adolescents as monotherapy or adjunct therapy	Clinical studies ongoing	Clinical studies ongoing
Key clinical trial design summary			
Monotherapy			
Trial name	SOLO 1 and SOLO 2: Ph3 monotherapy in adult M/S AD vs PBO [NCT02277743; NCT02277769][76,127]	ARBAN: Ph2 OL, monotherapy study in adult M/S AD vs TCS BID [NCT02465606]	NA
Trial design			
Duration	16 wks	12 wks (TCS during run-in followed by TCS withdrawal in tx group)	
Dosing	300 mg Q2W	125 mg Q4W	
Sample size	N = 1379 (SOLO 1 and 2)	N = 55	
Age	≥18 yrs	18-75 yrs	
Key inclusion/exclusion criteria	• Chronic AD ≥3 years • IGA ≥3 (5-pt scale) • EASI ≥16 • BSA affected ≥ 10% • Pruritus NRS ≥3	• M/S AD ≥1 year • IGA ≥3 (5-pt scale) • EASI ≥14 • BSA affected ≥10% • Pruritus VAS (from SCORAD) ≥3	
Primary endpoints	IGA 0/1 (%)+ ≥2 pt reduction, wk 16	TEAE (%)	
Combination therapy studies			
Trial name	CHRONOS: Ph3 R, DB study + TCS vs PBO + TCS [NCT02260986][128]	TREBLE Ph2: R, DB study + TCS [NCT02340234][129]	Ph2 study in adults with M/S AD [NCT02347176][85]
Trial design			
Duration	52 wks (BID moisturizer and concomitant TCS or TCI rescue [topical, systemic or phototherapy] permitted after wk 2)	12 wks (TCS during run-in followed by TCS BID)	12 wks (2-wk TCS run-in period)
Dosing	300 mg Q2W	125 mg SD, 250 mg SD, 125 mg Q4W	45 mg Q2W, 150 mg Q2W, 300 mg Q2W
Sample size	N = 740	N = 209	N = 204
Age	≥18 yrs	18-75 yrs	18-75 yrs
Key inclusion/exclusion criteria	• Chronic AD ≥3 years • IGA ≥3 (5-pt scale) • EASI ≥16 • BSA affected ≥10% • Pruritus NRS ≥ 3	• M/S AD ≥1 year • IGA ≥3 (5-pt scale) • EASI ≥ 14 • BSA affected ≥10% • Pruritus VAS (from SCORAD) ≥3	• M/S AD ≥1 year • IGA ≥3 (6-pt scale) • EASI ≥12 • BSA affected ≥10% • SCORAD ≥25
Primary endpoints	EASI 75 (%) and IGA 0/1 (%) at wk 16	EASI 50 (%) at wk 12	EASI 50 (%) at wk 12 IGA 0/1 (%) + ≥2 pt reduction, wk 12

AD, atopic dermatitis; BID, twice daily; BSA, body surface area; DB, double-blind; EASI, Eczema Area and Severity Index; EASI 50, ≥50% improvement in EASI from baseline; EASI 75, ≥75% improvement in EASI from baseline; IGA, Investigator's Global Assessment; IGA 0/1, "clear"/"almost clear" with ≥2-point improvement; IL, interleukin; M/S, moderate to severe; NA, not available; NRS, numeric rating scale; OL, open label; PBO, placebo; Ph, phase; pt, point; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomized; SCORAD, Scoring of Atopic Dermatitis; SD, single dose; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; VAS, visual analogue scale; wk, week; yrs, years.

3.2 | Other biologics in development

As AD is characterized by dysfunction in multiple immune pathways (types 1, 2, 17 and 22), a number of biologics in development target key effectors (eg cytokines, cytokine receptors) of these biological responses (Table **4**). While some of the novel biologics have shown promising clinical data for the treatment of AD, additional prospective studies are warranted to confirm efficacy and safety.

3.3 | Small molecule inhibitors

Beyond biologics, several small molecule inhibitors are in various stages of clinical development. For example, promising results

TABLE 4 Other key biologics in development for AD

Target	Pathophysiological Role	Pipeline Activity	Comments

IL-17A	Expression of the key Th17-related cytokine, IL-17A, is increased in acute AD lesions, along with infiltration of IL-17–positive cells into these lesions[130,131]	Secukinumab: a human IgG1κ, anti–IL-17A monoclonal antibody administrated subcutaneously
		• Phase 2 (moderate-to-severe AD)
		  • A 52-week pilot study (NCT02594098) is completed
		  • A 16-week randomized controlled trial (Secu_in_AD [NCT03568136]) is underway
			Secukinumab is FDA-approved for moderate-to-severe plaque psoriasis, active psoriatic arthritis and ankylosing spondylitis; results in AD trials have not yet been reported

IL-17C	Member of IL-17 family of cytokines that is produced at high levels in AD, induced by bacterial stimuli and may be involved in a pathogenic amplification loop that links the cutaneous microbiome with induction of IL-17–driven inflammation[132,133]	MOR106: a human IgG1, anti-IL-17C monoclonal antibody administered intravenously • Phase 2 (moderate-to-severe AD) • Under investigation in a randomized controlled trial (NCT03568071)	In a phase 1 study (NCT02739009), 83% of patients in the high-dose group achieved ≥EASI 50 by week 4[134]
IL-12 and IL-23	IL-12 and IL-23 are upregulated in AD lesions and drive differentiation of Th1 and Th17 cells, respectively[135]	Ustekinumab: a human IgG1κ, anti–IL-12/IL-23p40 monoclonal antibody that inhibits type 1 and type 17 immune responses through the targeted inhibition of the p40 subunit that is shared by these inflammatory cytokines[45] • Phase 2 (moderate-to-severe AD) • Despite completion of a 16-week, phase 2 study (NCT01806662) in adults with moderate-to-severe AD, further clinical development is unclear[136,137]	Non-significant improvements in SCORAD 50, the primary endpoint, were noted; effects may have been obscured by background TCS effects or insufficient ustekinumab dosing[136]
IL-22	The key type 22 cytokine, IL-22, contributes to epidermal hyperplasia and inhibits keratinocyte differentiation[58,138]	Fezakinumab: an intravenous, human IgG1λ, anti-IL-22 monoclonal antibody • Phase 2 (moderate-to-severe AD) • A phase 2a randomized controlled trial (NCT01941537) in adults with moderate-to-severe AD; development of the biologic is ongoing, though no phase 3 trials are planned as of February 2019[137]	The primary efficacy endpoint, decline in SCORAD index at week 12, non-significantly favoured fezakinumab (13.8 vs 8.0; $P = 0.134$), but the improvement was significant in the severe AD subset (21.6 vs 9.6; $P = 0.010$)[139]
IL-31	Produced by Th2 cells and mature dendritic cells and functions to evoke itch;[74,140,141] also alters expression of barrier proteins[142]	Nemolizumab: a humanized IgG2κ, anti-IL-31Rα monoclonal antibody that mitigates IL-31–dependent processes by antagonizing its cognate receptor • Phase 2 (moderate-to-severe AD) • A two-part, phase 2b randomized controlled trial (NCT01986933) in adults inadequately controlled by topical treatments[143] and a randomized controlled trial in adults receiving concomitant topical corticosteroids (NCT03100344) have completed	In part B of this study, improvements in pruritus VAS were maintained/increased at week 64, and change in EASI score ranged from -68.5% to −78.9% in the various nemolizumab dosing arms[143]

IL-33	An IL-1 family member which enhances type 2 responses through the induction of IL-5 and IL-13 in ILC2, type 1 responses through induction of IFN-γ, and also contributes to epidermal barrier dysfunction by down-regulation of filaggrin expression[144]	ANB020: a humanized IgG1, anti–IL-33 monoclonal antibody
		• Phase 2 (moderate-to-severe AD)
		  • Completed phase 2a proof-of-concept trial in moderate-to-severe AD
		  • A phase 2b randomized controlled trial (ATLAS [NCT03533751]) is ongoing as of March 2019
		PF-06817024: an anti–IL-33 monoclonal antibody
		• Phase 1 (moderate-to-severe AD)
		  • A phase 1 randomized controlled trial (NCT02743871) is ongoing as of March 2019
			ANB020: In a phase 2a proof-of-concept trial, 12 of 12 patients achieved at least EASI 50 by day 57[145]
			PF-0681724: No results have been reported to date

(Continues)

TABLE 4 (Continued)

Target	Pathophysiological Role	Pipeline Activity	Comments

Thymic stromal lymphopoietin (TSLP) receptor	TSLP is highly expressed in skin epithelial cells in AD and has known roles in generating type 2 immune responses and inducing itch in AD[137,146-148]; its cognate receptor, TSLPR, is expressed on multiple immune cells, including T cells, B cells, dendritic cells, mast cells, basophils and eosinophils[146]	Tezepelumab: a human IgG2λ, anti-TSLP monoclonal antibody
		• Phase 2 (moderate-to-severe AD)
		  • Completed phase 1 (NCT00757042) and phase 2a (ALLEVIAD [NCT02525094]) randomized controlled trials in adults with moderate-to-severe AD
		  • Development is ongoing, though no phase 3 trials are planned as of March 2019[137]
			A company press release noted that tezepelumab did not meet statistical significance for the phase 2a primary efficacy endpoint (EASI 50);[149] no further results have been reported

OX40	Expression of OX40, a tumour necrosis factor receptor family member, and its ligand OX40L is increased in AD lesions;[150] affects T-cell proliferation, survival and memory cell formation,[151] can cause autoreactive T cells to acquire pathogenic effector functions,[152] though no direct correlation with disease severity has been established[150]	KHK4083: a fully human, non-fucosylated IgG1, anti-OX40 monoclonal antibody
		• Phase 2 (moderate-to-severe AD)
		  • Completed phase 1 open-label study (NCT03096223)[153]
		  • Phase 2 randomized controlled trial in adults inadequately controlled by topical treatments is ongoing as of March 2019
		GBR 830: a humanized anti-OX40 monoclonal antibody
		• Phase 2 (moderate-to-severe AD)
		  • Completed phase 2a randomized controlled trial (NCT02683928)
		  • Phase 2b dose-ranging study is ongoing as of March 2019 (NCT03568162)
			KHK4083: No information currently available
			GBR 830: 17 of 23 evaluable patients (74%) had a ≥50% reduction in EASI score at week 4; study not powered to detect differences between GBR 830 and placebo groups[154]

IgE	Increased levels of serum immunoglobulin E (IgE) are commonly detected in AD patients, but its role in pathophysiology is not clear[2]	Omalizumab: humanized IgG1κ monoclonal antibody • Phase 4 (children with severe recalcitrant atopic eczema) • A phase 4 study (NCT02300701) is ongoing in children (ie 4 to 19 years) with severe recalcitrant atopic eczema as of March 2019[137,155]	Two systematic reviews found clinical benefits for omalizumab in selected patients with AD;[156,157] results for NCT02300701 have not yet been reported

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; EASI 50, ≥50% improvement in EASI from baseline; FDA, Food and Drug Administration; IFN, interferon; IgG, immunoglobulin G; IL, interleukin; ILC, innate lymphoid cell; SCORAD, Scoring of Atopic Dermatitis; TCS, topical corticosteroids; Th, T helper cell; VAS, visual analogue scale.

with the oral JAK1 inhibitor upadacitinib were reported from a phase 2b, 88-week, randomized controlled trial (NCT02925117), which prompted FDA breakthrough therapy for adults with moderate-to-severe AD, in January 2018. Several phase 3, randomized, controlled clinical trials are planned in adolescent and adults (ie 12-75 years) with moderate-to-severe AD, including two replicate studies of once-daily upadacitinib monotherapy (NCT03569293 and NCT03607422) and one combination study with topical corticosteroids (NCT03568318). In addition, phase 2 results with the once-daily, oral JAK1/JAK2 inhibitor baricitinib[88] (NCT02576938) have led to multiple phase 3 studies in adults with moderate-to-severe AD. These include replicate, 16-week randomized controlled trials (BREEZE-AD1 [NCT03435081] and BREEZE-AD2 [NCT03334422]), a 52-week, long-term safety and efficacy study (BREEZE-AD3 [NCT03334435]), a 16-week, randomized controlled trial (BREEZE-AD5 [NCT03334396]) with 116-week open-label extension (BREEZE-AD6 [NCT03559270]), and a randomized controlled trial in adults who had inadequate response to, intolerance to, or were contraindicated for cyclosporine (BREEZE-AD4 [NCT03428100]). Lastly, PF-04965842, an oral JAK1 inhibitor, has completed a phase 2 study (NCT02780167) and is under investigation in phase 3 trials in patients aged 12 years and older with moderate-to-severe AD. Studies include replicate, 12-week, randomized controlled trials (JADE Mono-1 [NCT03349060] and JADE Mono-2 [NCT03575871]) and a 96-week, long-term extension study (JADE EXTEND [NCT03422822]).

Another set of small molecule inhibitors, which have been investigated for the treatment of AD, include those targeting phosphodiesterase-4 (PDE-4), an enzyme involved in chronic inflammatory pathways. Inhibition of PDE-4 increases levels of cyclic adenosine monophosphate (cAMP), which mediates downstream events culminating in the inhibition of inflammatory cytokine secretion (eg IL-12, IL-17, IL-23, IFN-γ).[89] Though several PDE-4 inhibitors (eg apremilast, roflumilast) have not had clinical success to date, topical crisaborole was FDA-approved in December 2016 for the treatment of mild-to-moderate AD in patients aged 2 years and older.[90]

3.4 | Developing and differentiating therapies: biomarkers of treatment response

AD is a heterogeneous disease, both clinically and biologically, as several subtypes of AD have been recognized (ie intrinsic/extrinsic, adult/paediatric, ethnic origin), which differ in prevalence and clinical features.[49,53,91–95] Biomarkers may help clarify AD diagnosis by defining endotypes, subsets of patients with common underlying mechanisms of disease.[96] Biomarkers could be useful for screening those at high risk of AD before clinical disease appears and might aid in the early diagnosis of AD.[97] Beyond its diagnostic potential, the development of biomarkers in AD will allow more accurate assessment of disease severity than current methods, which require subjective inputs and for which there are currently many different composite indices. Studies of biomarkers for AD severity have recently begun to appear, but to date validated biomarkers for AD severity are lacking.[98,99] The availability of such biomarkers would allow quicker and more accurate assessment of treatment effects, the quantification of subtle clinical effects in patients where the disease phenotype is less visually evident, and, by providing a common standard, would minimize some of the uncertainties in cross-trial comparisons.[100] The integration of biomarker data in AD drug development, as was done in psoriasis, could help identify effective treatment approaches and drive promising agents forward.[47,101,102]

Importantly, biomarkers predictive of treatment response would allow for improved patient selection and stratification for targeted agents in AD.[47] An example of the promise of this approach has been reported for lebrikizumab in asthma, where the mean increase in forced expiratory volume (FEV_1) relative to placebo was considerably higher in adults with high levels of periostin, a protein induced by the type 2 cytokines IL-4 and IL-13.[103] The identification of validated predictive AD biomarkers could thus allow for a more personalized treatment approach that minimizes the risk of clinical failure of targeted agents in unselected patient populations and the expense of novel agents in patients for whom they provide no benefit. In this regard, biomarkers may be central to future advancements in AD.[24,47] With this in mind, predictive biomarkers for therapeutic responses were defined in AD patients treated with anti–IL-22 therapy, perhaps opening the door to a predictive medicine approach in AD and beyond.[104,105] In this way, the implications of disease heterogeneity on treatment responses may be attenuated as patients could ultimately receive personalized therapeutic approaches to treat their AD.

4 | CLINICAL PERSPECTIVE

The importance of IL-4Rα in disease pathobiology, and therefore IL-4 and IL-13 which utilize the receptor for signalling, was validated by the demonstration of clinical efficacy for dupilumab in patients with AD.[45,76,77,106] Yet, debate continues regarding which of these cytokines is most central to pathophysiology, or whether blocking both is required for a clinical response. Ongoing and future clinical and research studies will help to definitively address this question. Although further studies are warranted, the initial success of lebrikizumab and tralokinumab suggests that IL-13 blockade may be sufficient for achieving responses in AD patients.

The inclusion of biomarker analyses in clinical trial designs may improve outcome assessments and comparison of therapeutics, particularly biologics. One such option may be a predictive serum biomarker signature that represents a reliable and objective measure of disease severity not vulnerable to intra- or interrater variability.[24,25,32,107] Skin and serum biomarkers, which would ideally have utility in the near future, may be used to predict therapeutic responses to various treatments.[104] Furthermore, defining the disease remnant after successful treatment response may provide higher resolution in comparing treatment responses and identify drugs that are best at minimizing the "molecular scar" after treatment.[108,109] Improved understanding of the immune landscape in AD has stimulated the development of promising, novel therapeutic agents. Future incorporation of biomarkers in treatment response predictions may help transform the treatment paradigm of AD and the ability to generate meaningful and lasting responses, including cures.

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CONFLICTS OF INTEREST

MM is a consultant for Dermira. FC is an employee of Dermira. JLH is an employee of Dermira. EG is a consultant for AbbVie, Anacor, Celgene, Celsus Therapeutics, Dermira, Galderma, Glenmark, Janssen Biotech, LEO Pharmaceuticals MedImmune, Novartis, Pfizer, Regeneron, Sanofi, Stiefel/GlaxoSmithKline, Vitae, Mitsubishi Tanabe, Eli Lilly, Asana Biosciences and Kiowa Kirin; is an investigator for Celgene, Glenmark, Leo Pharmaceuticals, MedImmune, Regeneron, Eli Lilly; is a member of advisory boards for Celgene, Celsus Therapeutics, Dermira, Galderma, Glenmark, MedImmune, Novartis, Pfizer, Regeneron, Sanofi, Stiefel/GlaxoSmithKline, Vitae and Asana Biosciences.

AUTHOR CONTRIBUTIONS

MM, FC, JLH and EG participated in gathering and analysis of the data, participated in writing and revising the paper, and have all read and approved the final manuscript.

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