

What's New in Atopic Dermatitis



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KEYWORDS

- Atopic dermatitis • Crisaborole • Dupilumab • Tralokinumab • Lebrikizumab • Fezakinumab
- GBR 830 • JAK inhibitors

KEY POINTS

- Atopic dermatitis (AD) is increasingly common, and it lacked effective, safe, long-lasting treatments for many years.
- Recently, novel understandings of AD pathogenesis revealed AD has a complex, heterogeneous molecular fingerprint among different age groups and ethnicities, with a dominant helper T-cell (T_H)2/T_H22 skewing and variable T_H17/T_H1 overexpression.
- These findings led to rapid developments of numerous agents studied in clinical trials for AD. Few are already approved and available for clinical use.
- New topical agents for AD include phosphodiesterase 4 inhibitor, JAK (Januse kinase) inhibitors, and commensal bacteria.
- Systemic agents include targeted monoclonal antibodies, antagonizing T_H2/ T_H22/T_H17-related cytokines, and broad-acting systemic therapeutics, including JAK inhibitors and histamine 4 receptor antihistamines.

INTRODUCTION

Atopic dermatitis (AD), perhaps the most common inflammatory skin disease, with an increasing prevalence worldwide, is characterized by chronic symptoms of eczema and pruritus.¹ The quality of life of AD patients is significantly impaired, with higher prevalence of sleep disturbances, anxiety, depression, and even suicidal ideation compared with the general population.² Of AD patients, up to 20% are classified as moderate to severe by various clinical measurements, with the SCOring

Atopic Dermatitis (SCORAD), the Eczema Area and Severity Index (EASI), and the Investigator Global Assessment (IGA) most commonly used.³ Current therapeutics for extensive AD are lacking and consist of broad, nonspecific treatments, providing symptomatic and temporary relief with significant and prevalent adverse-effects.^{1,4,5}

In the past few years, extensive research shed light on the pathogenesis of the disease, allowing better understanding of the immune dysregulations causing the clinical outcome of AD. As was the case for psoriasis, which represents the best

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existing model for translational studies dermatology, this translational revolution led to the development of numerous new treatment methods for AD.⁶

It is difficult to write a “what is new in AD” review because this field is so rapidly evolving. This article reviews the new era of AD, with the latest discoveries in the pathogenesis of AD, leading to the developments of novel topical as well as systemic—both broad-acting and specific—agents for the disease.

PATHOPHYSIOLOGY

Traditionally, AD was considered a helper T-cell (T_H 2/ T_H 1 disease, with T_H 2 activation characterizing acute lesions and primarily T_H 1 skewing in chronic lesions.⁷ Recent extensive translational investigations have shown, however, that AD is strongly T_H 2/ T_H 22 centered throughout its course, with some T_H 1 and T_H 17 overexpression.^{7,8} The onset of acute AD skin lesions is characterized by large increases in T_H 2/ T_H 22-related cytokines and chemokines and some T_H 17-related signals.⁹ Later in the disease, intensification of these axes as well as T_H 1 augmentation orchestrates the chronic phenotype.^{7,10}

The pathogenic contribution of each pathway to the clinical presentation of AD across its various disease phenotypes is still not fully determined, because AD encompasses different clinical subtypes and molecular phenotypes.^{9,11–13} AD subtypes that were characterized immunologically so far as relatively T_H 17-dominant include the Asian-origin AD, intrinsic AD (approximately 20% of the patients, typically having normal serum IgE levels and lacking personal or familial atopy),¹² and pediatric AD.^{11–14} It is important to point out that despite having T_H 17-related up-regulations, these AD subtypes still have robust T_H 2/ T_H 22 activation, differing them from psoriasis, which is primarily T_H 17 skewed. Recently, African Americans with AD were shown largely T_H 2 and T_H 22 skewed, lacking T_H 1 activation.¹⁵ A lack of T_H 1 activation has also been seen in pediatric AD, perhaps arguing against a pathogenic role for this axis in AD.^{13,16}

The identification of the inflammatory pathways underlying AD has led to the development and testing of a new set of targeted and broad therapeutics for AD.

Due to the central role of T_H 2 activation in the disease, anti- T_H 2 drugs were developed early, and the first monoclonal antibody to be approved for the treatment of moderate-to-severe AD, dupilumab, is an antagonist of this pathway.^{17–20}

Because AD has a complex immune fingerprint, however, with diverse phenotypic subtypes among different subpopulations and a response of EASI-90 (90% improvement) to dupilumab seen in approximately 30% of patients,¹⁸ other therapeutic targets, in the T_H 22 and T_H 17 axes, as well as broad-acting agents, are also being studied.

TOPICAL TREATMENTS

Topical therapy is an important component of AD care, even in these times of newly introduced highly effective systemic drugs. The topical treatment is used for barrier repair and delivery of anti-inflammatory compounds, and the mainstay of disease management includes generous use of emollients and moisturizers. For many years, the only active topical agents used as an anti-inflammatory were topical corticosteroids and calcineurin inhibitors. As the treatment paradigm of AD expands, however, new topical drugs are also introduced.

The first drug to be licensed, crisaborole, is a phosphodiesterase (PDE) 4 antagonist. In AD, elevated PDE activity was found compared with normal skin.^{21,22} PDE hydrolyzes cyclic adenosine monophosphate (cAMP) and results in up-regulation of inflammatory mediators. PDE antagonism acts in a broad, nonspecific mechanism, because it elevates intracellular cAMP; thus, downstream inhibition of numerous proinflammatory factors ensues.²¹

Crisaborole 2% topical ointment is indicated in adults and children over 2 years of age with mild-to-moderate AD. The ointment showed statistically significant efficacy, with 51.7% and 48.5% of patients achieving Investigator's Static Global Assessment scores of clear or almost clear, respectively, during phase III clinical trials.²³ Crisaborole 2% also improved other AD symptoms, including pruritus,²³ and showed tolerability in sensitive anatomic skin locations, including the face/hairline, genitalia, and intertriginous areas, where treatment with topical corticosteroids is often avoided due to adverse effects.²⁴ Overall, the ointment was well tolerated with limited adverse events, most commonly application-site pain, burning, or stinging.^{23,24}

Another promising group of topical agents, now in clinical trials for AD, are the Janus kinase (JAK) inhibitors. The JAKs, a family of tyrosine kinases (TYKs), including JAK1, JAK2, JAK3, and TYK2, phosphorylate the intracellular domain of several cytokine receptors to facilitate the attachment and stimulation of the signal transducer and activator of transcription (STAT), which then enters

the nucleus and effects transcription.²⁵ As discussed later, these are being tested as systemic treatment of AD, but topical formulations had also shown efficacy in phase II trials. In a 4-week clinical trial of tofacitinib, the ointment showed robust and significantly greater efficacy versus placebo.²⁶ Nevertheless, topical tofacitinib for AD has not progressed past phase II trials. JTE-032, a topical JAK inhibitor that antagonizes all 4 receptor-associated kinases, markedly and rapidly improved clinical signs and symptoms in 327 Japanese adult AD patients, with a favorable safety profile.²⁷ Other topical JAKs are being investigated in clinical trials in the pediatric population and adults, including topical ruxolitinib in phosphate cream (ClinicalTrials.gov: NCT03257644 and NCT03011892). A dual SYK/JAK inhibitor, cerdulatinib, is also anticipated to be tested for AD.

A different possible topical therapy relies on another aspect of AD pathophysiology, the disrupted skin microbiome of AD patients. During flares, the diversity of the bacteria that normally reside on the skin is reduced, and there is a shift toward *Staphylococcus aureus* colonization.²⁸ *S aureus* has an important pathogenic role in AD, because it perpetuates the inflammation, specifically T_H2-related, and further compromises skin barrier. Autologous microbiome transplant in 1 study and application of commensal gram-negative bacteria in another led to decreased colonization of *S aureus*, with clinical improvement and reduced used of topical corticosteroids in the second study.^{28,29}

These data suggest newer topical nonsteroidal agents may play an important role as primary therapy or as adjunctive steroid-sparing therapy for AD in the near future and will expand the current limited variety of topical therapy given for AD.

SYSTEMIC TARGETED AGENTS—HELPER T-CELL 2 ANTAGONISTS

Dupilumab, Tralokinumab, and Lebrikizumab

Cytokine-targeted drugs currently are an important therapeutic tool in dermatology, and because AD is largely T_H2/T_H22 centered, antagonizing these axes have strong rationale for AD treatment.

Dupilumab is a fully human monoclonal antibody inhibiting both interleukin (IL)-4 and IL-13 signaling, by blocking their common IL-4 receptor- α (IL-4R α). Due to the key pathogenic role IL-4 and IL-13 play as initiators and drivers of the T_H2 axis, blocking both cytokines has strong anti-T_H2 effects. Elevated IL-4/IL-13 levels disrupt skin barrier by inhibiting lipids, tight junctions, and antimicrobial peptide formation; interrupting

keratinocytes differentiation; and initiating and propagating *S aureus* colonization.^{28,30,31} IL-4/IL-13, therefore, have a major part in perpetuating AD, both molecularly and clinically.

In stage II and III clinical trials of dupilumab versus placebo in AD patients, dupilumab was significantly more effective in all primary and secondary outcome measures.^{17–19} Furthermore, recent meta-analyses of these trials,^{32,33} including more than 2400 adult AD patients, showed dupilumab was consistently more effective than placebo and had an acceptable, placebo-like safety profile. Only local injection side reactions and conjunctivitis occurred as specific side effects of dupilumab.^{32,33} The pathogenesis of this conjunctivitis is yet to be elucidated.³⁴ Coupled with these clinical score improvements, expression of T_H2-related markers was reduced as were markers of epidermal hyperplasia, immune cells infiltrates in the skin, and T_H17/T_H22 activity. Dupilumab also improved the expression of genes of epidermal differentiation, barrier function, and lipid metabolism and suppressed T_H2-related serum biomarkers.²⁰

Except dupilumab, which almost entirely blocks T_H2 activation, there are also exclusive anti-IL-13 agents being investigated for AD: tralokinumab and lebrikizumab, both of which are fully humanized monoclonal antibodies.

Tralokinumab binds 2 different receptors: the heterodimeric receptor, composed of IL-4R α (targeted by dupilumab) and IL-13R α 1, and the IL-13R α 2 decoy receptor, which results in lower cytokine levels.³⁵ Tralokinumab is now in phase III clinical trials for asthma and AD (NCT03363854). In asthma, predictive biomarkers for tralokinumab efficacy were serum dipeptidyl peptidase 4 and periostin, which correlate with increased IL-13 activity. The same biomarkers were monitored in the AD phase II clinical trial. In this trial, different doses were studied in 204 AD adult patients with concomitant topical corticosteroids. Here, the highest applied dose of tralokinumab led to significant improvements in clinical scores versus placebo, yet high placebo responses were seen, probably due to concomitant topical corticosteroid application. The drug was overall well tolerated. Similarly to asthma, greater, significant responses were found in the subpopulation with high concentrations of IL-13-related biomarkers, suggesting these markers have predictive value for the efficacy of anti-IL-13 therapy in AD patients.³⁶

Lebrikizumab binds the soluble IL-13 at an epitope that strongly overlaps with the binding site of IL-4R α ³⁷ and is also investigated for asthma as well as for AD (NCT03443024) and other conditions. It was studied in proof-of-concept phase II

study on adults with AD in combination with mandatory topical corticosteroids.³⁸ At 12 weeks, significantly more patients achieved a 50% reduction of the severity score EASI (EASI-50) with lebrikizumab, although pronounced placebo responses were seen, speculatively due to the topical corticosteroid use. It was concluded that protocol-mandated topical corticosteroid limited investigators' ability to fully evaluate lebrikizumab's efficacy in AD. The drug was well tolerated.³⁸

These positive data raise the possibility that narrow IL-13 targeting may also be a valid future therapy for AD, and clinical trials investigating these drugs as monotherapy are needed.

Interleukin 31 Blockers

Despite the suggested pivotal role of IL-4/IL-13 in AD, skin lesions of AD are characterized by robust up-regulations of various other T_H2 -related cytokines and chemokines, and these too have the potential of being therapeutic targets.^{7,9}

Nemolizumab, another monoclonal antibody, antagonizes IL-31 receptor A and thus blocks IL-31 signaling on various cells, including peripheral neurons.³⁹ IL-31, a T_H2 -related cytokine, also known as the itch cytokine, is significantly up-regulated in AD lesions.^{40,41} In addition, cytokine levels correlate with disease severity, and up-regulated IL-31 was shown to compromise epidermal-barrier function, perpetuating the well-documented itch-scratch cycle of AD.^{40,41} Notwithstanding, despite the possible potential of anti-IL-31 targeting, a phase II randomized, double-blind, placebo-controlled study of nemolizumab for AD showed improvements in clinical scores but did not reach statistical significance. Nemolizumab did significantly decrease pruritus scores and had an overall satisfactory safety profile.³⁹

Clinical trials for another anti-IL-31 monoclonal antibody, BMS-981164, were terminated at an early stage (NCT01614756). Thus, the role of IL-31 antagonism in AD treatment is still to be elucidated, because it is not clear if the effects include only symptomatic, antipruritic relief.

Inhibitors of the Thymic Stromal Lymphopoietin–OX40 Axis

The T_H2 pathway also includes the thymic stromal lymphopoietin (TSLP)–OX40 axis, which is speculated to initiate the allergic response and is referred as the master switch of allergic inflammation.^{42,43} Through the effects of this axis on dendritic cells, Langerhans cells, and mast cells, T_H2 -skewed responses ensue, and $CD4^+$ T-naïve

cells are activated to produce IL-4, IL-13, and IL-5.^{43,44} OX40 ligand (OX40L) is downstream to TSLP and was shown to deepen T_H2 polarization and maintain chronic allergic inflammation.^{45,46} IL-33 is an amplifier of the TSLP–OX40L axis and was also shown to directly disturb skin barrier in AD by down-regulating *FLG* expression.^{47,48} TSLP, its receptor, OX40L, and IL-33 are significantly up-regulated in lesional AD skin,^{47,49} providing another possible therapeutic targets for AD.

Tezepelumab, a monoclonal antibody antagonizing TSLP, failed in a phase II clinical trial for AD (NCT02525094),⁵⁰ and MK-8226, a TSLP receptor antagonist (NCT01732510), was terminated due to business reasons. An OX40 antagonist, GBR 830 (NCT02683928), showed efficacy in a phase II clinical trial after 2 intravenous doses. Significantly more GBR 830-treated patients versus placebo achieved EASI-50 after more than 2 months, a long-lasting effect despite the convenient and minimal dosing. The drug was well tolerated.⁵¹ KHK4083, another OX40 inhibitor, is being investigated in a phase I open-label clinical trial for AD in Japan (NCT03096223).⁵² An anti-IL-33 monoclonal antibody, ANB020, showed efficacy in a small, proof-of-concept, phase II clinical trial of adult AD patients.⁵³ Because OX40 and IL-33 inhibitors show promise, future studies are anticipated. TSLP inhibitors may, speculatively, emerge in the future as treatments of very early AD, due to its role in disease onset.

TARGETING HELPER T-CELL 22

In addition to common T_H2 skewing across all AD subtypes, T_H22 -related genes are also overexpressed, and the main cytokine in this axis, IL-22, plays a major role in barrier function disruption, by down-regulating terminal differentiation and tight junction products, and promotes epidermal hyperplasia resulting in acanthosis.^{54–56} IL-22 is significantly up-regulated in AD lesions and has been correlated to disease severity and clinical response to various AD treatments.^{57–63}

An anti-IL-22 antibody, fezakinumab, showed numerical efficacy that did not reach significance in a randomized, double-blind, placebo-controlled trial for AD as a monotherapy.⁶⁴ Despite these somewhat disappointing results, subanalyses of only severe AD patients revealed significance response to fezakinumab over placebo.⁶⁴ A mechanistic study of fezakinumab showed the drug's effects were stratified depending on baseline IL-22 expression, with molecular response present only in high baseline IL-22 patients, perhaps opening the door to a personalized medicine approach

for AD.⁶⁵ In addition, similarly to dupilumab, significant down-regulations of multiple immune pathways, including T_H1, T_H2, T_H17, and T_H22, were found in patients with high IL-22 levels treated with fezakinumab.⁶⁵ Fezakinumab was well tolerated, and the most common adverse events were viral upper respiratory tract infections.⁶⁴

These data suggest fezakinumab may serve as an agent for severe AD patients or for patients with unsatisfactory response to T_H2 inhibition by dupilumab,⁶⁴ yet reliable predictors for drug efficacy still need to be validated in larger, extended studies.

HELPER T-CELL 17/INTERLEUKIN 23 ANTAGONISM

As discussed previously, in addition to the common T_H2/T_H22 overexpression, some AD phenotypes (including Asian AD, intrinsic AD, and pediatric AD) show higher T_H17-related markers expression as well as histologic features that are also seen in psoriasis, which is T_H17/T_H1 driven.^{66,67}

IL-23 prompts both T_H17 and T_H22, and, downstream to IL-23, IL-17 with IL-22 stimulates tissue inflammation and barrier defects.⁶⁸ In addition, IL-23 is significantly decreased after AD treatments,^{57–60,62} providing a rationale for IL-23 antagonism in AD.

Ustekinumab, a monoclonal antibody antagonizing the p40 subunit of IL-23 and IL-12, is highly efficacious for psoriasis.⁶⁹ For AD, however, despite several reports of refractory AD responsive to ustekinumab treatment,^{70,71} a phase II clinical trial of ustekinumab showed numerical improvements in clinical scores but did not reach statistical significance over placebo.⁶¹

As for IL-17, the IL-17 family consists of 6 members, IL-17A–F.⁷² IL-17A and IL-17F are products of activated lymphocytes, and IL-17E and IL-17C are products of epidermal keratinocytes and other nonimmune cells.⁷³ Nevertheless, IL-17A and IL-17C share some features, as keratinocytes respond to these cytokines in a similar manner.^{73,74} In addition, there is a robust connection between IL-17A and IL-17C, because IL-17A induces IL-17C in keratinocytes, and, in turn, IL-17C can induce IL-17A production in T lymphocytes. This relationship can be viewed as part of the feed-forward mechanism in the epidermis, in which amplification of cellular immune responses results from overexpression of cytokines and chemokines produced by keratinocytes.⁷⁵

IL-17A inhibition by drugs, such as secukinumab, a monoclonal antibody that selectively inhibits IL-17A and is highly efficacious in

psoriasis,⁷⁶ is being tested for AD in a phase II clinical trial (NCT02594098).

The interest in IL-17C is growing, as overexpression of IL-17C was found in skin lesions of both psoriasis and AD compared with control skin, and, with other data suggesting IL-17C has a pathogenic role as a central mediator of inflammation in both diseases, antagonism of IL-17C seems to be an appealing strategy.^{73,74}

A phase I clinical trial of an anti-IL-17C monoclonal antibody, MOR106, showed encouraging clinical results in AD, with approximately 80% of drug-treated patients achieving EASI-50 compared with less than 20% in the placebo group, with a favorable safety profile.⁷⁷ This positive yet small, early-phase, proof-of-concept trial necessitates further studies (now recruiting, NCT03568071), preferably in larger cohorts of AD and across different AD phenotypes, to reveal the potential of IL-17C antagonism in subpopulations with higher T_H17 activity.

BROAD-ACTING SYSTEMIC AGENTS

Even though narrow-targeted agents in AD proved that blocking 1 cytokine may have a much broader effect on immune dysregulations, including upstream to the antagonized cytokine, broad-acting agents are another important possible tool in the armamentarium of AD treatments.

Janus Kinase Inhibitors

The JAK-STAT, as discussed previously, mediates T_H2 polarization in addition to a range of other intracellular immune dysregulations.⁷⁸ Oral JAK inhibitors are small molecules that block these intracellular signaling and result in a potent, broad, inhibition of various inflammatory pathways as well as antiproliferative activity.⁷⁹

Currently, 3 JAK inhibitors are studied in clinical trials for AD: baricitinib, a JAK 1 and JAK 2 antagonist; upadacitinib, a JAK1 antagonist; and PF-04965842 (abrocitinib), another specific JAK1 inhibitor.

Baricitinib is the first JAK inhibitor to show efficacy in a phase II trial for AD⁸⁰ and is now in ongoing phase III trials (NCT03435081). With baricitinib, significantly more patients achieved EASI-50 compared with placebo (61% vs 37%) at 16 weeks, and the proportion of baricitinib-treated patients achieving EASI-50 compared with placebo was significant as early as week 4.⁸⁰ The drug was well tolerated, yet more adverse events occurred in the baricitinib-treated group, with headache, increased blood creatine phosphokinase, and nasopharyngitis.⁸⁰

Upadacitinib showed impressive and significant clinical efficacy in a phase II clinical trial for AD. In the upadacitinib group, approximately 50% of patients achieved EASI-90, and the same percentage attained IGA of clear or almost clear skin, with a good safety profile, as presented in the 2018 American Academy of Dermatology meeting (NCT02925117).⁸¹ Peer-reviewed publication is still pending.

A third JAK inhibitor, PF-04965842 (abrocitinib), was also investigated in a phase II clinical trial for AD and showed promising results as assessed by the IGA score at week 12, with responses of up to 45% in drug-treated group compared with 6% in the placebo group.⁸² A phase III trial for PF-04965842 is now recruiting (NCT03349060).

Histamine 4 Receptor Antihistamines

Other broad-acting, oral, small molecules, representing an additional promising treatment option for AD, are the histamine 4 receptor (H₄R) antihistamines. Unlike the H₁R-blocking antihistamines that traditionally are used as antipruritic agents, yet with effects in AD patients relying mostly on their sedative properties,⁸³ H₄R antihistamines have implications relevant to AD pathogenesis. H₄R is highly expressed on keratinocytes in lesional skin of AD patients, and its stimulation promotes keratinocyte proliferation and inhibits their differentiation, impairs skin barrier, and induces pruritus.^{84,85} A phase II clinical trial of ZPL-3893787, an H₄R antagonist, is ongoing (NCT02424253).

SUMMARY

Despite a highly prevalent disease, until recently AD lacked effective, safe, long-term treatment options for moderate-to-severe patients. Now, however, it is somewhat challenging to keep up with the extremely rapid pace of developments in AD. Recent data revealing the molecular underpinnings of AD, together with the huge unmet need for efficacious, safe therapies, and vigorous industry interest in developing new medications,¹ led to the current exciting era of numerous therapeutics investigated for the disease. Novel agents—topical and systemic, narrow targeted and broad acting—will be introduced to AD management in the near future and will revolutionize the treatment paradigm of the disease.

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