# Addressing Unmet Needs in Atopic Dermatitis: Evaluating Disease-Modifying Capabilities of Current and Emerging Therapies

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***Abstract:*** **Atopic dermatitis (AD) is a highly burdensome inflammatory skin condition affecting nearly one-quarter of the pediatric population and often continuing into adulthood. Despite recent advancements in systemic therapies providing temporary symptom relief over the past decade, AD frequently remains difficult to control, necessitating increased dosages or alternative treatments due to recurrent disease. This review synthesizes current literature to identify unmet needs of treating AD beyond medication-related limitations and evaluates existing therapies for their efficacy in modifying underlying disease mechanisms. Key findings include variability in AD pathophysiology and phenotypes across different age groups and ethnicities, indicating a need for research into endotype-specific treatments. The literature also comprises evidence suggesting that select current drugs, such as targeted biologics and Janus Kinase (JAK) inhibitors, may offer long-term disease-modifying benefits. Future management strategies should explore novel approaches, including manipulation of the microbiome, immune response, and neural function, as these may lead to additional improvements in AD treatment and long-term symptom relief.**

## Capsule Summary

- The unmet needs of treating atopic dermatitis (AD) may be driven by various pathophysiological mechanisms across patient populations.
- Biological agents and Janus kinase (JAK) inhibitors may be viable options for long-term relief.
- Emerging therapies for AD place emphasis on manipulation of the microbiome, immune dysregulation, epidermal barrier, and neural function, which may lead to alteration of AD disease processes.

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## INTRODUCTION

Atopic dermatitis (AD), is the most common chronic inflammatory skin disease, with up to 25% of children and 2–5% of adults being impacted.[1–3] The onset of disease largely occurs within the first year of life, with 90% of cases appearing by 5 years of age.[4] While the majority of pediatric patients will grow out of their condition, at least 10–30% continue to suffer into adulthood, and a small subset may develop new diseases as adults.[5] Poorly controlled disease and a myriad of atopic and non-atopic comorbidities have a substantial impact on patients' health-related quality of life.[6]

The therapeutic ladder for managing AD has undergone significant expansion in the last several years as pathophysiology unravels new pathways. While patients with AD may report temporary relief, symptoms usually recur, requiring increased dosage or an alternative regimen. For those patients who appear to respond well over a prolonged period, it is unclear whether they will require lifelong treatment. Standardized guidelines for classifying therapies

as disease-modifying for AD could be beneficial in this regard.[7] The following sections will explore the challenges of treating AD that have been discussed in the literature thus far and uncover avenues for continued research. Furthermore, current and emerging treatments will be analyzed for their benefit in providing temporary alleviation of symptoms as opposed to their potential for long-term pathophysiological modifications and disease remission.

## UNMET NEEDS OF TREATING AD

Despite significant progress in uncovering the pathogenesis and treatment possibilities for AD, there remains a gap in translating this knowledge into everyday patient care. Traditional topical medications for the management of AD are often used as part of a regimen to manage rather than cure AD. These treatments may include a host of moisturizers, emollients, corticosteroids, calcineurin inhibitors, and others. Escalation to systemic therapy is considered when the AD is refractory to topical treatments, or a large body surface area is involved. Previously, immunosuppressants such as methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil, were the agents of choice, especially for severe disease. However, the action of these agents is wide-ranging and their limited safety profile curtails their suitability for prolonged use.[8] The recent development of novel treatments such as Janus Kinase (JAK) inhibitors and biologics has dramatically improved the management of AD and offers the potential for long-standing effects and durability. Nonetheless, even with evolving regimens, patients continue to suffer from their disease.

In a study combining patient surveys with healthcare claims data, 81.3% of adults diagnosed with AD within the last 5 years who were treated with systemic agents reported at least 1 flare within a month of completing the survey.[9] During these flares, the disease burden was reported to be similar to the overall burden in patients with severe AD, regardless of baseline severity.[9] This high rate of flare recurrence may point to inadequately controlled underlying disease, poor treatment adherence, or suboptimal timing of treatment, and supports unmet therapeutic needs.[10–13]

In chronic skin conditions such as AD, patients often stray from treatment plans due to inconvenience, fear of medication ineffectiveness, and uncertainties about potential side effects.[14,15] In patient discussions, a frequent worry is whether continuous medication is necessary. AD patients, often young, are hesitant about long-term dependency on medication, particularly due to overall safety risks. Such concerns are especially pronounced among young women considering pregnancy and older patients on multiple medications.[16,17] Likewise, clinicians may be reluctant to prescribe certain medications to female patients of childbearing age due to concerns about the safety of both the mother and the fetus.[18] The quest for disease-modifying therapies is thus critical. Such treatments would ideally offer a finite course that effectively alters the disease trajectory, allowing patients to discontinue therapy after some time without the risk of disease recurrence.

### Is AD One Disease?

AD may present with heterogeneous phenotypes and altered molecular signatures across different populations.[19] Morphologically, pediatric AD more often presents with acute inflammatory involvement of the face, trunk, and extensor limbs, while adults may have lichenified lesions in a flexural distribution.[20] Despite certain shared pathogenic features across AD phenotypes, such as enhanced T helper (Th) 2 axis, the immune signatures/endotypes may differ across age and ethnic groups, or according to the status of filaggrin (FLG) mutations, and IgE expression.[21]

The evolution of the adult AD phenotype and the cytokines involved in the disease process undergo change as patients age, as demonstrated in recent studies. For instance, skin-homing (CLA+) Th1 cells were significantly less expressed in infants with AD compared with older patients.[22] In contrast, systemic (CLA-) T-cell frequencies steadily increased after infancy, suggesting that disease chronicity may be associated with systemic immunity.[22] Further, the frequencies of interleukin-22 (IL-22) were normal in infants but significantly higher in adolescents and adults, while IL-9 frequencies were selectively increased in adolescents with AD.[22] In addition, pediatric patients (younger than 5 years) with early AD (within 6 months of disease onset) have a psoriasis-AD Th17/Th2 blended immune profile, demonstrating that certain patient populations may benefit more than others from therapies targeting specific immune pathways.[23] The endotypic diversity across age groups underlines the importance of exploring different targeted therapies based on the age of patients with AD.

The phenotypes and endotypes of AD also vary across ethnic groups. For example, the levels of the hyperplasia-inducing cytokine, IL-22, are increased in the serum of Asian patients with AD, while the serum levels of Th1-related markers are lower compared with those of European American descent.[21,24] Asian patients with AD exhibit higher levels of Th17-related cytokines in the skin compared to European American adults.[21] In contrast, the AD endotype in African American patients is characterized by attenuated Th17-related markers along with Th1 markers.[25] In African American patients with AD, genomic studies have shown that FLG loss-of-function mutations are not prevalent, but are associated with the persistence of AD.[26–28] Of note, the prevalence of AD is higher in patients of Asian (7–10%) and African American (19%) background, further emphasizing the importance of considering targeted therapies specific to these populations that are greatly affected.[29–32]

Currently, AD is predominantly approached with a one-size-fits-all regimen. These data underscore the unmet need to address differing phenotypes and endotypes of AD within the

clinical setting, ideally while aiming to develop precision-driven therapeutic strategies.[21]

## DISEASE-MODIFYING POTENTIAL OF TREATMENTS FOR AD

Even with significant advances in understanding the pathogenesis of AD and the drugs currently approved, many patients still cannot attain a clear or nearly clear state after treatment cessation.[33–39] The ultimate goal of the therapeutic pipeline, thus, will be to develop disease-modifying, endotype-tailored, targeted treatments that will provide long-lasting remission, and perhaps cure, to AD.[40]

## Current Therapies

### *IL-4 and IL-13 Inhibitors*

There are currently three biological treatments for AD that are approved by the United States Food and Drug Administration (FDA): dupilumab, tralokinumab, and most recently, lebrikizumab.[41,42] Dupilumab targets IL-4 receptor-α (IL4R α) which inhibits IL-4 and IL-13 signaling (Fig. 1).[43] Tralokinumab and lebrikizumab antagonize IL-13 specifically.[44] While these biologics target specific cytokines, they enhance multiple factors involved in AD pathogenesis, including the epidermal barrier, inflammation, itch components, and microbial diversity.[41,45] Moreover, in dupilumab-treated patients, there is a positive

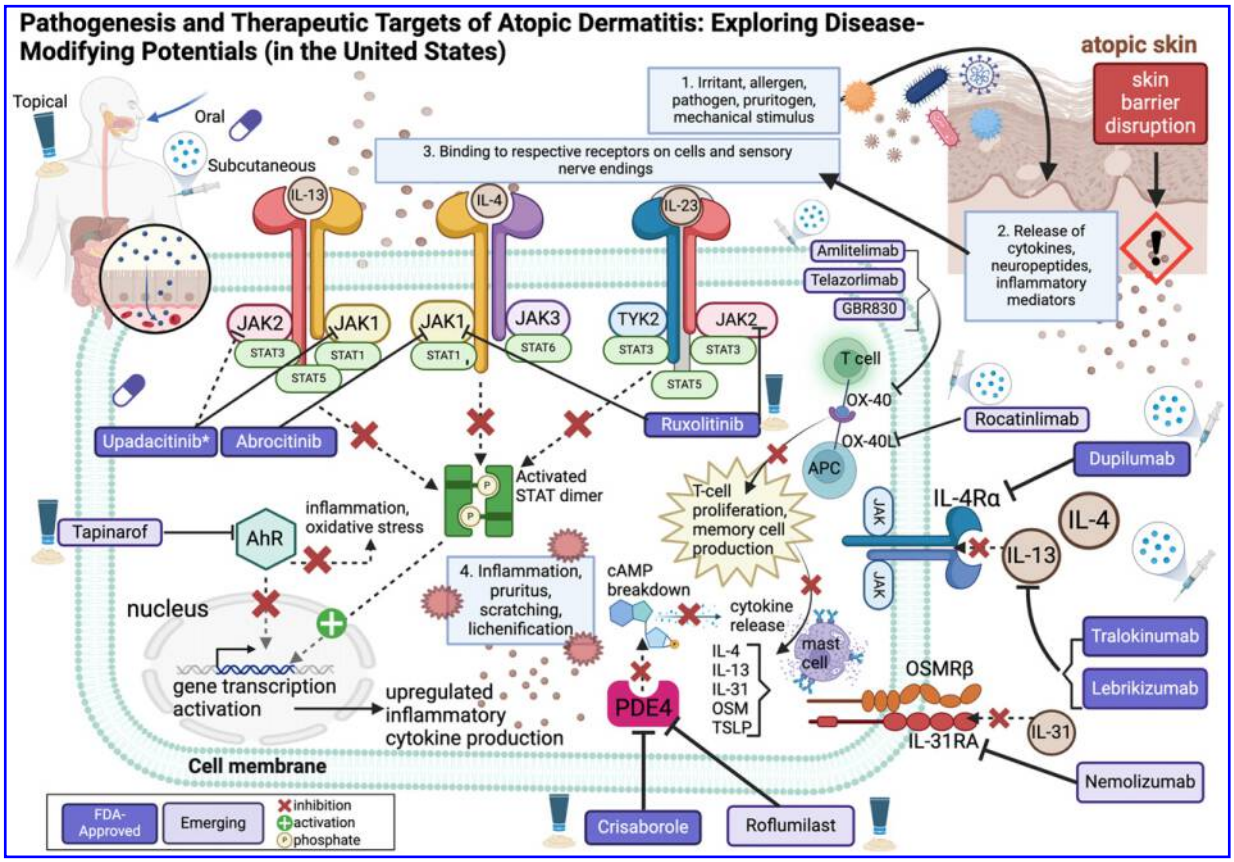


**Figure 1.** Pathogenesis and therapeutic targets of atopic dermatitis: exploring disease-modifying potentials (in the United States). Targeted treatments for AD may be administered orally, topically, or subcutaneously, and function by inhibiting specific points within the complex pathophysiological web. JAK inhibitors hinder the downstream activation of STAT dimers, preventing the activation of gene transcription within the nucleus and altering the regulation of inflammatory cytokine production. Likewise, AhR inhibitors, such as Tapinarof, interfere with gene transcription. PDE4 inhibitors, such as crisaborole and roflumilast, increase intracellular cAMP levels by inhibiting this enzyme, leading to the suppression of pro-inflammatory cytokines. Amlitelimab, telazorlimab, and GBR830 inhibit the OX40 receptor on T cells, while rocatinlimab inhibits the OX40 ligand on antigen-presenting cells. Disruption of the co-stimulatory OX40-OX40L inhibits the promotion, expansion, and survival of effector and memory T cells, as well as T cell differentiation toward pro-inflammatory T helper subsets. Dupilumab blocks the IL-4 receptor alpha subunit, thus inhibiting the signaling of both IL-4 and IL-13, key drivers of the type 2 inflammatory response in AD. Tralokinumab and lebrikizumab similarly block this response by selectively inhibiting IL-13. Nemolizumab is a monoclonal antibody that blocks the signaling of two relevant cytokines in AD by binding to the IL-31 receptor A: IL-31 (pruritus) and OSM (skin inflammation). AD, Atopic dermatitis; IL, Interleukin; AhR, aryl hydrocarbon receptor; JAK, Janus Kinase; STAT, signal transducer and activator of transcription proteins; cAMP, cyclic adenosine monophosphate; APC, antigen-presenting cell; OSMRβ, oncostatin M receptor beta, OX40-L, OX40 ligand; P, phosphate; PDE4, phosphodiesterase 4. *Upadacitinib has greater inhibitory action against JAK1 compared to JAK2.

correlation between molecular changes and clinical improvement.[40] In a retrospective study of 22 adults treated with dupilumab, more than half of the patients achieved remission lasting about 40 weeks following treatment discontinuation.[46] Several real-world studies have been performed evaluating the long-term efficacy of dupilumab for up to 3 years, however, the majority of patients involved in these studies remained at least partially on dupilumab for this duration.[47,48] These findings support the hypothesis that dupilumab may modify the underlying disease pathology of AD. Nonetheless, additional large-scale studies are needed to further investigate this possibility.

### *JAK Inhibitors*

JAK inhibitors are one of the few available treatments that may alter the mechanisms underlying AD and modify the disease. The JAK family is composed of four non-receptor tyrosine kinase (TYK) members: JAK1, JAK2, JAK3, and TYK2.[49] Each JAK has a different function and distinct cytokines that rely on its signaling, many of which are implicated in AD.[50–52] JAK inhibitors not only disrupt cytokine signaling but have also been shown to regulate FLG.[53] Clinically, this leads to restoration of the skin barrier, decreased skin thickening, and alleviation of itch.[53] There are currently three FDA-approved JAK inhibitors for AD: one topical (ruxolitinib), and two oral agents (abrocitinib and upadacitinib).[54] Ruxolitinib cream functions by blocking the ATP-binding catalytic site on the JAK 1 and JAK 2 enzymes.[55] Abrocitinib selectively targets JAK1, while upadacitinib inhibits both JAK1 and JAK2, with a stronger predilection for JAK1.[54,56] As opposed to current biologics which target specific cytokines, JAK inhibitors harbor the benefit of hindering the downstream effects of multiple cytokines at once.

There is some early evidence demonstrating the potential long-term impact of JAK inhibitors in patients with AD. In one study, JAK inhibitors were added as a rescue therapy for patients with AD who experienced recurrence on dupilumab.[57] Upadacitinib or tofacitinib were used in combination with dupilumab for 2–6 months before being discontinued. Interestingly, cessation of JAK inhibitors after 2 to 6 months of treatment led to maintenance of disease control with no recurrence, although the period of monitoring was only 3–4 months.[57] One potential rationale for this is that the blockade of a single immune axis may not lead to persistent remission in patients with AD. However, by inhibiting the JAK-STAT signaling pathways involved in relevant families of cytokines, there is potential for true disease modification.[52] In a larger trial of 798 AD patients who responded to therapy with 200 mg abrocitinib over 12 weeks, the impact of random withdrawal or dose reduction was tested.[58] During a 40-week maintenance period, 80.9% of patients who were withdrawn from abrocitinib treatment experienced a disease flare, compared with 42.6% of patients who were randomly reduced to 100 mg abrocitinib and 18.9% of patients who continued on 200 mg.[58] The sustained efficacy of systemic JAK inhibitors, abrocitinib, and upadacitinib, may depend on the length of initial treatment, although further investigation is needed.[54,57,58] Whether the efficacy of JAK inhibitors is maintained after withdrawal following long-term treatment remains unknown.[54] Future translational studies will have to determine if JAK inhibitors alter the immune signature of AD over time.

## Emerging Topical Therapies

### *Topical Aryl Hydrocarbon Receptor (AhR) Agonists*

The AhR is present in various skin cells like keratinocytes and dendritic cells and can be activated by numerous compounds. Its activation plays a role in mediating epidermal differentiation and reducing inflammation.[59] Tapinarof is a high-affinity AhR agonist that regulates gene expression, leading to the abatement of type 2 inflammation, downregulation of oxidative stress, and skin barrier repair.[60] In addition, the AhR system plays a role in upregulating FLG and loricin.[61] Tapinarof cream was approved by the FDA for the treatment of plaque psoriasis in May 2022 and is currently undergoing phase III studies for AD.[62,63] In a 12-week double-blind phase IIb trial involving adults and adolescents with AD (NCT02564055), treatment with 0.5% or 1% tapinarof cream twice a day showed significant improvement in eczematous lesions and itch compared to vehicle [Investigator's Global Assessment (IGA) score improvement of 58% vs 24% in the vehicle].[60] In a phase IIb multi-center trial studying the effect of tapinarof 0.5% or 1% once or twice a day in patients with psoriasis, the primary endpoint was met with sustained improvement 4 weeks after discontinuation of the treatment.[64] Furthermore, following the completion of two subsequent phases III studies, psoriasis patients who had received tapinarof 1% once a day for 12 weeks had the option to enter a 1-year open-label extension study, in which they would remain off treatment until those with a PGA score of 0 at week 12 relapsed to two or more. The mean length of time to recurrence was more than 4 months.[65] These results, albeit in psoriasis, illuminate the potential long-term benefits of modifying the AhR pathway. However, long-term withdrawal studies are needed to assess its duration of efficacy in AD and to compare its effectiveness with placebo or topical steroids.

### *Topical Phosphodiesterase 4 (PDE4) Inhibitors*

PDE4 has long been a therapeutic target of interest in AD. PDE4 is an intracellular enzyme impacting epithelial integrity and inflammation through cyclic adenosine monophosphate (cAMP) degradation.[66] Inhibiting PDE4 leads to increased cAMP levels, which downregulates NFκB, a key modulator of cytokine production like IL-4, IL-5, and IL-10.[62] This reduction in cytokine production and T-cell activation leads to anti-inflammatory effects.[67] Crisaborole ointment was approved in 2016 for mild-to-moderate AD. Two new PDE4 inhibitors,

roflumilast and difamilast, are now also being studied for mild-to-moderate AD.[62,68] Notably, roflumilast has a potency 25–300 times greater than that of crisaborole, which may lead to enhanced duration and strength of impact in AD.[69,70] This topical therapy may modify the disease process of AD by regulating the downstream effect of Th2 overactivation, however, there is not enough data available to confirm its long-term impact and length of remission upon treatment cessation.[71]

## Emerging Biological Agents

### *Lebrikizumab*

The most recent addition to the US market is an IgG4k monoclonal antibody named lebrikizumab, as mentioned previously. This systemic therapy targeting the Th2 pathway of AD specifically prevents the formation of the IL-4Rα-IL-13Rα1 (IL-13Rα1/IL-4Rα) heterodimer receptor signaling complex by binding to IL-13 (IL-13).[79] The safety and efficacy of lebrikizumab were studied in multiple phase III clinical trials. Results have shown that lebrikizumab at a dosage of 250 mg every two weeks yielded greater efficacy compared to placebo in adolescents and adults with moderate-to-severe AD by week 16.[80,81] Data gathered from ADvocate1 and ADvocate2, including responders at week 16, indicated that at week 52, 71.2% of patients on lebrikizumab Q2W, 76.9% on lebrikizumab Q4W, and 47.9% on placebo (lebrikizumab withdrawal arm) maintained IGA 0 or 1 with a ≥2-point improvement from baseline. Patients of 78.4% and 64.0% on lebrikizumab Q2W, 81.7% and 66.4% on lebrikizumab Q4W, and 66.4% and 41.9% on lebrikizumab withdrawal arm, sustained EASI 75 and EASI 90, respectively. Patients of 84.6%, 84.7%, and 66.3% in the respective treatment arms also maintained a ≥4-point decrease in the pruritus numeric rating scale (NRS).[82] The lack of substantial drop-off in drug efficacy suggests that lebrikizumab may be disease-modifying.[83,84]

### *Nemolizumab*

Another medication that has gone through clinical trials in both adolescents and adults is nemolizumab, an immunoglobulin G (IgG)2κ antibody against IL-31 receptor A (IL-31RA). nIL-31 is a key cytokine in itch and correlates with AD severity.[72] In a double-blinded phase III clinical trial (NCT01986933), participants were randomly assigned to receive either nemolizumab or a placebo.[73] The primary endpoint was pruritus assessed by the visual analog scale (VAS) after 16 weeks. The nemolizumab group showed a significantly greater reduction in VAS score (−42.8% vs −21.4%) compared to placebo. However, the change in the Eczema Area and Severity Index (EASI) score was not significant.[73] In a meta-analysis of randomized clinical trials (RCTs), nemolizumab significantly reduced pruritus VAS and EASI scores compared to placebo.[74] Nemolizumab may offer the benefit of treatment response over extended periods of time. In a late-breaking presentation in March 2024, results from the phase III ARCADIA clinical trials were reported, showing that AD patients treated with nemolizumab who had successful skin and itch responses at 16 weeks maintained the benefits through week 48, despite a dose reduction from every 4 to every 8 weeks.[75] These data are promising tokens of the potential long-lasting impact of this up-and-coming biological.[76] Of note, nemolizumab was recently approved for the treatment of adults with prurigo nodularis and was granted priority review by the FDA for AD.[77,78]

### *OX-40/OX-40L*

OX-40 and its ligand OX-40L, belonging to the tumor necrosis factor (TNF) receptor superfamily, are costimulatory molecules that play critical roles in T-cell activation, survival, clonal proliferation, memory cell production, and apoptosis suppression.[85–87] The activation of T cells is critical to the process of chronic inflammation in AD. These proinflammatory signals originate from antigen-presenting cells (APCs). OX-40 is found on T cells within skin lesions of AD, while the OX-40 ligand is expressed on APCs. The binding of OX-40L stimulates the production of Th2 cytokines.[88,89] Various new compounds are under development to target this pathway.[87]

One such agent is the fully humanized IgG1 anti-OX40L antibody rocatinlimab (AMG451/KHK4083), which is undergoing phase III trials for adults with moderate-to-severe AD. Of note, rocatinlimab depletes activated T cells by inducing antibody-dependent cellular cytotoxicity.[90] In a recent phase IIb study, the most effective dosage was 300 mg every 2 weeks at week 16 resulting in a mean EASI reduction of 61%.[91] Rocatinlimab effectively reduced Th2/Th22 and pruritus-related moderators at week 16 and decreased Th2, Th1/17, and Th22-related genes through week 52 despite treatment cessation at week 36.[91] Telazorlimab is another anti-OX40 IgG1 monoclonal antibody that likely functions in a similar manner to rocatinlimab. This drug has recently completed phase II testing, during which 300 and 600 mg administered every 2 weeks led to a significant decrease in the EASI score compared to placebo (300 mg: −54.4% vs −34.2%; 600 mg: −59.0% vs −41.8%).[92]

Unlike rocatinlimab, amlitelimab is a fully human IgG4 monoclonal antibody targeting the OX40-L on APCs. As such, there is no direct depletion of T cells involved in its mechanism.[91] Amlitelimab is currently being investigated for its applicability to improving multiple chronic inflammatory diseases. A recently completed phase IIb study (STREAM-AD) evaluated a range of doses of amlitelimab in adults with AD inadequately controlled with topical medications. Results were reported in a late-breaking session in October 2023 and have generated enthusiasm for this potential best-in-class AD treatment.[93] Patients experienced up to a 61.5% improvement in EASI score after 16 weeks of treatment with subcutaneous amlitelimab, with continued improvement up to week 24. The second part of this trial consisted of a 28-week period during which treatment

with amlitelimab was continued or withdrawn. Late-breaking results were presented in March 2024 demonstrating sustained improvement of AD signs and symptoms both with (69.2%) and without (58.8%) continuation of amlitelimab as determined by maintained high EASI scores and IGA of 0/1.[94] Additionally, AD-related biomarkers (TARC, eosinophils, and IL-22) remained reduced at week 52 in both groups. This suggests that inflammatory T cells may be durably modified via OX-40L blockade. Phase III trials are anticipated to begin in 2024 and will assess the durability of response with quarterly dosing. If successful, amlitelimab could serve as a meaningful agent capable of changing the lives of patients suffering from AD.

These cumulative observations strongly suggest that OX-40 inhibitors may modify the mechanisms underlying AD. The excitement surrounding OX-40/OX-40L signaling has sparked the incorporation of other potential disease-modifying mechanisms as well, such as half-life extension technology, to further enhance the long-term impact of these agents in AD patients.[95] Upcoming longitudinal studies will need to ascertain if there is a sustained clearance of AD and if changes in AD pathogenesis align with the remission of the disease.

A summary of clinical trials investigating agents targeting the OX-40/OX-40L complex in AD is depicted in Table 1.

### AD Drugs Approved Outside the United States

Many other therapeutics have been approved for AD in other countries and are making their way to the US market as well. Among the topical therapies, delgocitinib ointment, a pan-JAK (JAK1/JAK2/JAK3/TYK2) inhibitor, was approved in Japan for moderate-to-severe pediatric and adult AD in January 2020.[96,97] Several phase III studies of topical delgocitinib focusing on chronic hand eczema are currently underway.[98] (NCT05355818, NCT04871711, NCT04872101, NCT05259722, and NCT0494984). Oral baricitinib, on the contrary, is a JAK1/JAK2 inhibitor that is approved for adults with moderate-to-severe AD in both Japan and Europe.[40,99] Baricitinib has been through multiple phase III trials, including the BREEZE-AD5 trial (NCT03435081), which focused on baricitinib monotherapy for moderate-to-severe AD.[100] In this study, 29.5% of patients taking baricitinib 2 mg achieved EASI75 compared to 12.9% in the 1 mg group and 8.2% in the placebo group.[100] Nemolizumab is indicated for AD-associated pruritus in patients aged 13 years and older in Japan, and lebrikizumab was approved in Europe in November 2023 for AD patients at least 12 years of age.[82,101–105]

## OTHER EMERGING TREATMENTS

A summary of interventions for the management of AD that are actively undergoing investigational trials for their impact on the skin microbiome, immune system, neural function, and stress response is depicted in Table 2.

### Microbiome Manipulation: Exploring Novel Therapeutic Approaches

AD is characterized by the predominance of *Staphylococcus aureus* (*S. aureus)* and reduced bacterial diversity.[106] The technique of microbiome manipulation is undergoing extensive research for its use in AD. Through the use of topical or intestinal agents, this strategy aims to reduce the overgrowth of *S. aureus* and/or help restore commensal *Staphylococcus* species.[85] The microbiome may be scientifically altered through a variety of approaches, ranging from transplantation, bacteriotherapy over the skin, and use of pre-, pro-, and post-biotics.[45]

One of the most exciting emerging concepts is fecal microbiota transplantation (FMT). FMT is the process of transferring the functional gut microbial community from healthy donors to patients with certain disease states to restore gut microbiota homeostasis.[107] There is a growing body of evidence supporting the role of gut microbiota in the progression of AD.[108] The potential use of FMT in AD patients is in the very early stages of exploration. In a study assessing the effect of FMT on AD-skin lesions in a mouse model, FMT was able to positively modulate gut microbiota and aid in the recovery of AD-related inflammation.[108] Given these preliminary studies, the translation of FMT from bench to bedside is a plausible method to potentially alter the course of AD.

Bacteriotherapy performed over the skin may also be an effective method for restoring the microbiome in patients with AD. Topical niclosamide (ATx201), for instance, reduces *S. aureus* colonization and increases the microbial diversity of patients with AD in a phase II RCT.[109] In one double-blind RCT of 11 patients with AD, a topical cream formulated from a patient's own reintroduced coagulase-negative strain of *Staphylococcus* led to a 99.2% reduction in *S. aureus* along with clinical improvement of lesions.[110] Coal tar, which functions to induce antimicrobial peptide activity via activation of the aryl hydrocarbon, has been shown to significantly reduce *S. aureus* and *S. capitis* in AD patients with a complementary increase in the commensal *S. epidermidis* strain.[111] The role of orally administered probiotics in the management of AD has been highly controversial.[112,113]

### Altering the Immune Response

Controlling inflammation proactively in pediatric patients may modify the disease course, potentially attenuating the progression of the atopic march.[114,115] In a recent meta-analysis, the investigators sought to determine the impact of dupilumab on the rate of acquisition of allergic events compared to placebo. Strikingly, across 12 clinical trials with a median age of onset at 2 years old, the treatment of AD with dupilumab reduced the risk of new or worsened allergies by 34%.[116] These results provide evidence for the potential benefit of early intervention in altering the progression of AD and the atopic march.

**TABLE 1. Summary of Active Phase 2 and Phase 3 Clinical Trials for Studies on OX-40 or OX-40L Inhibitors for Atopic Dermatitis**

| Clinical Trials.gov ID | Phase | Agent / Target | Abbreviated Name | Design | Status |
|---|---|---|---|---|---|
| NCT05769777 | 2 | Amlitelimab / OX-40L | ATLANTIS | Single group, 1-arm, long-term study evaluating the safety and efficacy of subcutaneous amlitelimab for treatment of participants aged ≥12 years with Mod-Sev AD | Recruiting |
| NCT05492578 | | | RIVER-AD | Single group, long-term extension study to assess the safety and efficacy of amlitelimab in adult participants with Mod-Sev AD previously enrolled in an amlitellimab clinical trial up to 120 weeks | Recruiting |
| NCT06224348 | | | SHORE | Parallel group, multicenter, randomized double-blind placebo-controlled study to measure the efficacy and safety in participants aged ≥12 years with Mod-Sev AD on background TCS. | Recruiting |
| NCT06407934 | 3 | Amlitelimab / OX-40L | ESTUARY | Multinational, multicenter, randomized double-controlled, placebo-controlled, parallel 48-week extension study evaluating the treatment response and safety of two dose regimens of amlitelimab compared with withdrawal in participants ≥12 years with Mod-Sev AD | Recruiting |
| NCT06130566 | | | COAST 1 | Multinational, multicenter, randomized double-controlled, placebo-controlled, parallel study to evaluate the efficacy and safety of two doses of subcutaneous amlitelimab compared to control in participants aged ≥12 years with Mod-Sev AD | Recruiting |
| NCT06181435 | | | COAST 2 | Multinational, multicenter, randomized double-controlled, placebo-controlled, parallel study to evaluate the efficacy and safety of two doses of subcutaneous amlitelimab compared to control in participants aged ≥12 years with Mod-Sev AD | Recruiting |
| NCT06241118 | | | AQUA | Parallel group, multinational, multicenter, randomized, double-blind, placebo-controlled study for the treatment of participants aged 12 years and older with Mod-Sev AD that inadequately responded to prior biological or oral JAK inhibitor therapy | Recruiting |
| NCT05633355 | 3 | Rocatinlimab / OX-40 | ROCKET- Orbit | Open-label, 52-week study to assess the safety, tolerability, and efficacy in adolescent subjects aged ≥12 to <18 years with Mod-Sev AD | Active, not recruiting |
| NCT05651711 | | | ROCKET-Horizon | Randomized, 24-week, placebo-controlled, double-blind study to assess the efficacy, safety, and tolerability in adult subjects with Mod-Sev AD | Active, not recruiting |
| NCT05398445 | | | ROCKET-Ignite | Randomized, 24-week, placebo-controlled, double-blind study to assess the efficacy, safety, and tolerability in adult subjects with Mod-Sev AD | Recruiting |
| NCT05724199 | | | (ROCKET-SHUTTLE | Randomized, 24-weel, placebo-controlled, double-blind study to assess the efficacy, safety, and tolerability of rocatinlimab in combination with TCS and/or TCIs in adults with Mod-Sev AD | Active, not recruiting |

(*continued*)

**TABLE 1.** (*Continued*)

| Clinical Trials.gov ID | Phase | Agent / Target | Abbreviated Name | Design | Status |
|---|---|---|---|---|---|
| NCT05882877 | | | ROCKET-ASCEND | Multicenter, double-blind, maintenance study to assess long-term safety, tolerability, and efficacy of rocatinlimab in adult and adolescent subjects with Mod-Sev AD | Recruiting |
| NCT05704738 | | | ROCKET- ASTRO | Randomized, 52-week, placebo-controlled, double-blind study with rerandomization to assess the efficacy and safety of rocatinlimab as monotherapy and combination therapy in adolescent subjects | Recruiting |
| NCT06224192 | | | ROCKET- Outpost | Randomized, open-label study to assess successful self-administration of subcutaneous rocatinlimab | Recruiting |

*Mod-Sev, moderate-to-severe; TCS, topical corticosteroids; JAK, Janus Kinase.*



Targeting the alarmin, IL-33, and its receptor, ST2, is another promising strategy to affect early innate immunity mechanisms.[85] Upon release from keratinocytes, IL-33 downregulates FLG expression and promotes the activation of a wide range of Th2 mediators, including IL-4, IL-5, IL-13, the TSLP-OX40L axis, mast cells, and eosinophils.[117,118] Many targeted therapies have already entered clinical testing.[119–121] Additional potential targets for early disease modification include IL-25 and TSLP, as well as PDE4 and JAK signaling pathways.[40,122]

Adaptive immunity is kickstarted with antigen presentation and its role in triggering inflammation through various pathways.[85] T cells travel from the lymph nodes via alterations in the sphingosine 1-phosphate receptor (S1PR) or into the skin via the C-C chemokine receptor 4 (CCR4), illuminating two interesting blocking strategies.[85,123] CCR4 is highly expressed by Th2 cells, and antagonists against this receptor help prevent the expansion of Th2 and Th17 cells.[124] In a recent phase I study, CCR4 antagonist RPT193 was clinically effective in patients with moderate-to-severe AD.[125] Selective S1PR agonists have been successfully developed and approved for the treatment of multiple sclerosis. One of these agents, etrasimod, has undergone phase II testing in a double-blind RCT for its efficacy and safety in adults with AD. While the primary outcome was not met, the efficacy of etrasimoid as measured by physician and patient-reported outcomes was evident.[126] The disease-modifying potential of these treatments remains uncertain; however, their focus on critical pathways and molecules implicated in the pathogenesis of AD suggests the possibility of achieving long-term disease remission.

### Altering Neural Function and the Stress Response

The repeated scratching behavior in AD leads to dopamine-controlled habit learning and reward circuits in the brain.[127] The noradrenergic system also exhibits higher activity in patients with AD.[112] In combination with dopaminergic activity, this leads to stimulation of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent cortisol secretion.[127] The increased release of cortisol and noradrenaline in the neural circuits can disrupt the function of the dorsolateral prefrontal cortex, altering the perception of itch and perpetuating the habitual itch-scratch cycle.[127] Of note, chronic cortisol release due to scratching may contribute to the type-2 immune response, however, blunting of the HPA axis over time has been hypothesized to prompt the shift to shared type-2/type-1 dominated inflammation in later phases of AD.[127]

The role of neural distortion in AD, especially related to sleep, uncovers another potential avenue for targeted therapeutic intervention. Melatonin is secreted from the pineal gland and regulates stress response. AD patients have reduced secretion of melatonin, which correlates with scratching-induced sleeplessness. In two randomized placebo-controlled crossover trials, 4–8 weeks of nightly melatonin supplementation in children and adolescents led to a significant decrease in the Scoring AD (SCORAD) index, with a variable reduction in sleep-onset latency compared to placebo.[113,128] Cannabinoids and their receptors (CB1, CB2) are also involved in neuroprotection, cognition, and the stress response.[129] The specific role of these receptors warrants further investigation.[130] Psychological interventions may be another therapeutic approach to mediating changes to the neural system in AD. In a randomized clinical trial of 102 adults with AD, a 12-week therapist-guided cognitive behavior therapy (CBT) intervention led to significant symptom reduction.[131] These benefits remained 12 months after cessation of CBT, lending merit to its potential disease-modifying capacity.[131]

## CONCLUSION AND FUTURE DIRECTIONS

Recent advances have led to the development of therapeutics targeting key aspects of the AD pathway, significantly improving the prospects for tailored, disease-modifying treatments. There remains a critical need to identify precise intervention targets that could allow for sustained remission post-treatment, rather

**TABLE 2. Summary of Interventions for the Management of AD that are Actively Undergoing Investigational Trials for their Impact on the Skin Microbiome, Immune System, Neural Function, and Stress Response**

| Study Title | NCT# | Intervention | Relevant Outcome Measures[a] | Status |
|---|---|---|---|---|
| | | Microbiome | | |
| MB in AD under systemic therapy (BIO-AD) | NCT05099315 | Dupilumab, Cyclosporine, Baricitinib | -Microbial Composition of Skin [b] | R |
| SA and the skin MB during flare and resolution of AD | NCT05578482 | Dicloxacillin oral capsule / Elocon 0.1% cream | -Changes in the skin MB[c]<br>-Changes in the number of cytokines[c] | R |
| Assessment of the effects on the skin MB of amending an OTC Eczema product with activated oil | NCT05413395 | topical colloidal oatmeal w/modified plant oil | -Change in absolute abundance of SA on target lesion site[b]<br>-Change in Shannon Diversity Index between target lesion site and non-lesion site[c] | R |
| Effects of treatments on AD | NCT01631617 | Cephalexin, TMP/SMZ, Doxycycline | -MB alterations, measured by change in Shannon Diversity Indices[b] | R |
| Molecular signatures in inflammatory skin disease | NCT03358693 | Dupilumab<br>Tralokinumab<br>Baricitinib<br>Abrocitinib<br>Upadacitinib | -Changes of immune cell composition, transcriptome, proteome, and MB signatures | R |
| Efficacy of fecal microbial transplantation treatment in adults with AD | NCT0461303<br>NCT04283968 | Fecal microbial transplantation | -Change in the severity of atopic dermatitis after treatment with fecal microbial transplantation[b] | C / R |
| | | MICROBIOME & IMMUNE SYSTEM | | |
| Immunogenetic profiling of dupilumab for the treatment of AD | NCT03293030 | Dupilumab | -$CD4^+$ T effector cells expressing IL-4[b]<br>-Microbiome[c] | R |
| Vitamin D treatment effect for AD in children | NCT05523986 | Vitamin D | -Microbiome[b]<br>-Total IgE[b]<br>-Allergen-specific IgE[b] | R |
| | | MICROBIOME & EPIDERMAL BARRIER FUNCTION | | |
| Modified Huang-LianJie-Du decoction (MHLJDD) for AD in children | NCT05613062 | MHLJDD | -Microbiome[c]<br>-TEWL[c]<br>-Skin hydration[c] | R |
| Assessment of the effect of coconut and sunflower see oil derived isosorbide diesters and colloidal oatmeal | NCT05688735 | Isosorbide diesters (with 0.1% colloidal oatmeal) and topical hydrocortisone 2.5% | -TEWL[c]<br>-Skin hydration[c]<br>-Shift in skin microbiome[c] | R |
| | | NEURAL STRUCTURE AND FUNCTION | | |
| Mind and skin- A prospective cohort study evaluating the impact of inflammation, itch, and sleep disturbance on the brain, mental health and cognition, in patients with severe atopy | NCT05790330 | Observational-Dupilumab or methotrexate for severe eczema as per the usual standard of care | -Sleep (quality, morningness, and eveningness)[b]<br>-Brain activity during sleep[b]<br>-Movement during sleep (via watch and mattress sensors)[b]<br>-Resting brain state[b]<br>-Structural brain changes[b] | R |
| The effect of intervention and mechanism of internet CBT on chronic itching in patients with AD | NCT05502848 | -Internet-based CBT | -Change from baseline on scratching times[b]<br>-Change from baseline on structural MRI and functional MRI[b] | NYR |

(*continued*)

**TABLE 2.** (*Continued*)

| Study Title | NCT# | Intervention | Relevant Outcome Measures[a] | Status |
|---|---|---|---|---|
| Mediation in inflammatory dermatosis | NCT05500794 | STRESS RESPONSE -MSBR | -Quantification of inflammatory stress markers in saliva (α-amylase, cortisol, IL-6, IL-31, TNF-α)[c]<br>-Quantification of inflammatory stress markers in serum (CRP, cortisol, IL-6, IL-3, TNF-α, ACTH)[c] | R |

[a]*Limited to studies with primary or secondary outcomes measures pertaining to changes in the microbiome or epidermal barrier function.*
[b]*Primary outcome measure.*
[c]*Secondary outcome measure.*
*NCT#, National Clinical Trial Number; C, completed; R, Recruiting; NYR, not yet recruiting; SA, Staphylococcus aureus; TEWL, transepidermal water loss; OTC, over-the-counter; TMP/SMZ, Trimethoprim/sulfamethoxazole; MB, Microbiome; CBT, Cognitive Behavioral Therapy; MSBR, mindfulness-based stress reduction; CRP, C-reactive protein; ACTH, adrenocorticotropic hormone.*



than necessitating continuous therapy. Future studies should prioritize early intervention strategies within the disease's progression, aiming for primary prevention to potentially avert AD altogether, or to halt the atopic march following the onset of AD. In addition, the forthcoming years may witness the integration of genomic and epigenetic strategies in AD management, unlocking opportunities for personalized, disease-modifying, precision medicine.

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