doi.org/10.58931/cait.2025.5177

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Emerging Biologics in the Management of Atopic Dermatitis

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing and remitting inflammatory skin disease marked by intense pruritus that significantly impacts the daily activities and quality of life of those affected.[1] Topical therapies such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) have been the mainstay of treatment and may offer symptomatic relief. However, their efficacy is often suboptimal, they carry the potential for adverse effects, application adherence can be challenging, and they are not suitable for more widespread disease. Conventional systemic agents such as methotrexate and cyclosporine are used off-label for AD. However, these medications are associated with off-target toxicities and are generally unsuitable for long-term use due to safety concerns. Advances in understanding the immunopathogenesis of AD (**Figure 1**)[1-3] have led to the development of multiple new therapies. These include biological agents that target these pathways by neutralizing specific cytokines or their receptors. This paper will review the therapies that have been recently approved or are currently in various stages of development.

Targeting IL-13

Dupilumab and tralokinumab are well-established monoclonal antibodies that target Type 2 inflammatory cytokines. Dupilumab targets the interleukin (IL)-4Ra subunit, thereby inhibiting IL-4 and IL-13 signalling, whereas tralokinumab specifically targets the IL-13 cytokine. Both treatments have shown efficacy in improving the signs and symptoms of AD and have a favourable safety profile. Dupilumab is also approved for treating other Type 2 inflammatory conditions including asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis. More recently, the United States Food and Drug Administration (FDA) has also approved it for chronic spontaneous urticaria.[4]

Lebrikizumab is a high-affinity monoclonal antibody that neutralizes IL-13, and has recently been approved for treating moderate-to-severe AD in adolescents and adults in multiple regions. In phase 3 clinical trials[5,6] (ADvocate1, ADvocate2, and ADhere), lebrikizumab demonstrated improvements in AD signs, symptoms, and quality of life. It was well tolerated as monotherapy (ADvocate 1 and 2)[5] or in combination with

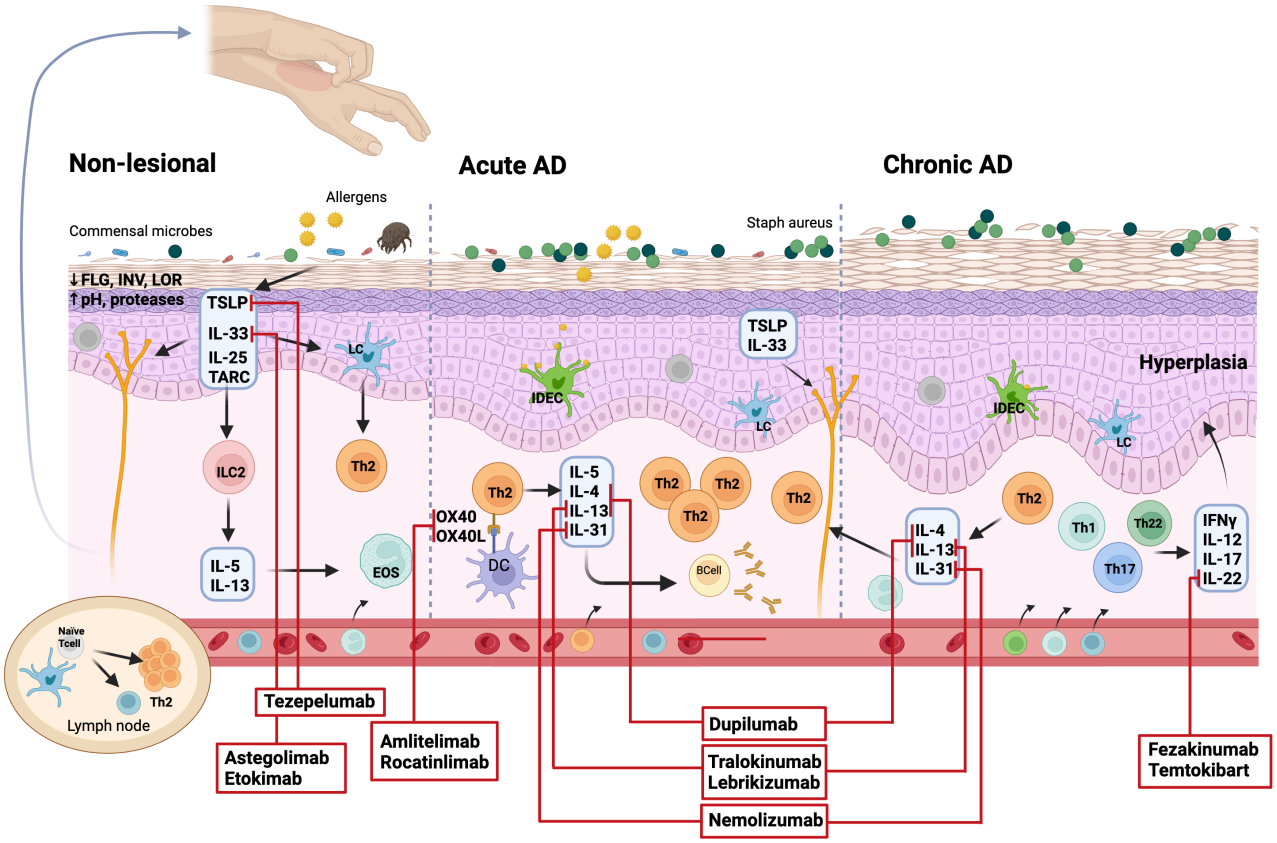

Figure 1. Immunopathogenesis of atopic dermatitis and biologic targets[1,3,4]; *created with www.biorender.com.*

Disruption of the epidermal barrier in AD triggers keratinocytes to release alarmins (e.g. TARC, IL-25, IL-33, TSLP), activating dendritic cells, ILC2s, and TH2 cells, which drive Type 2 immune responses, IgE production, and pruritus through interaction with sensory neurons. This immune cascade is further amplified by skin-homing T cells, eosinophils, and resident memory T cells, contributing to chronic inflammation, cutaneous remodelling, and neuroinflammation in later stages of disease (chronic AD).

Abbreviations: AD: atopic dermatitis, **EOS:** eosinophil, **FLG:** filaggrin; **IDEC:** inflammatory epidermal dendritic cells, **INV:** involucrin, **IgE:** immunoglobulin E, **IL:** interleukin, **ILC2:** group 2 innate lymphoid cells, **LOR**: loricrin, **TARC:** Thymus and activation-regulated chemokine, **Th:** T helper, **TSLP:** thymic stromal lymphopoietin.

TCS (ADhere).[6] In the ADvocate1 and 2 trials, lebrikizumab significantly improved skin clearance by week 16. A total of 43.1% of patients in ADvocate1 and 33.2% in ADvocate2 achieved an Investigator's Global Assessment (IGA) score of 0 or 1 with a ≥2-point improvement from baseline, compared to 12.7% and 10.8% in the respective placebo groups (P<0.001). Additionally, 59.3% (ADvocate1) and 51.9% (ADvocate2) of lebrikizumab-treated patients achieved a 75% or greater improvement in the Eczema Area and Severity Index (EASI-75) compared to 16.4% and 18.1%, respectively, in the placebo arms (P < .001). Further, the ADhere trial revealed that 41.2% of patients achieved the IGA endpoint versus 22.1% in the placebo + TCS group (P=0.01). Additionally, 69.5% of patients reached EASI-75 compared to 42.2% in the placebo+ TCS group (P=0.002).[6] Across all three trials, lebrikizumab was generally well tolerated. The most common adverse events included conjunctivitis, injection site reactions, and nasopharyngitis, most of which were mild to moderate in severity. Discontinuation rates were low and comparable to placebo.[5,6]

Targeting IL-31

Pruritus, the hallmark symptom of AD, develops due to the increased production of pruritogenic cytokines, such as thymic stromal lymphopoietin (TSLP), IL-4, IL-13, and IL-31. These cytokines are released by various cell types and activate histamine-independent itch pathways. The IL-31 signalling pathway is a suitable target in AD because IL-31 not only directly communicates with neurons responsible for transducing itch signals, but it also stimulates nerve elongation and neurite branching in the skin.[1,3]

Nemolizumab, an IL-31 receptor antagonist approved by the FDA to treat moderate-to-severe AD with associated pruritus, was studied in the pivotal trials ARCADIA 1 and ARCADIA 2.[7] These 48-week, double-blinded, placebo-controlled phase 3 studies evaluated nemolizumab, which was administered as a 60 mg subcutaneous loading dose at baseline, followed by 30 mg every 4 weeks. This treatment was given alongside background topical therapies (TCS, TCI) in adolescents and adults with moderate-to-severe AD.

For the primary endpoints, nemolizumab significantly improved IGA success and EASI-75 responses at week 16 compared to placebo. In the ARCADIA 1 trial, IGA success was achieved by 36% in the nemolizumab group versus 25% in the placebo group. Further, EASI-75 was achieved by 44% of those in the nemolizumab group versus 29% receiving placebo. Similar results were observed in the ARCADIA 2 trial.[7] For the key secondary endpoints, nemolizumab showed significant improvements in pruritus relief (≥4-point reduction in the Peak Pruritus Numerical Rating Scale [PP-NRS] score) as early as week 1, with these benefits sustained through week 16. Additionally, by week 16, nemolizumab also reduced sleep disturbances (≥4-point reduction in Sleep Disturbance Numerical Rating Scale [SD-NRS] score). Furthermore, nemolizumab led to higher proportions of participants achieving itch-free or nearly itch-free states (PP-NRS <2) and showed combined improvements in skin clearance and pruritus relief compared to placebo.[7] The safety profile was favourable, with rates of adverse events similar to those of the placebo group. Most reported adverse events were of mild-to-moderate severity, with the most common being worsening AD and asthma-related events.[7]

Targeting the OX40-OX40L Axis

OX40 is a costimulatory molecule that plays a key role in AD by promoting T-cell activation, differentiation, and survival through its interaction with OX40L (**Figure 1**). This pathway amplifies inflammation by driving the proliferation of Th2 cells and other T helper cell subsets (Th1, Th17, Th22) in AD. As a result, it impairs skin barrier function, sustains chronic inflammation, and contributes to AD progression and recurrence.[8] The OX40-OX40L pathway is being investigated as a target for managing AD through the use of monoclonal antibodies. Amlitelimab targets the OX40L, while rocatinlimab targets the OX40 receptor.[8]

A phase 2b randomized controlled 52-week trial evaluated amlitelimab in adults with moderate-to-severe AD. The trial compared four dosing regimens of amlitelimab (250 mg plus a 500 mg loading dose, 250 mg, 125 mg, or 62.5 mg) administered every 4 weeks versus a placebo. The primary endpoint showed least squares mean percentage changes ranging from -51.6% to -61.5% for the four amlitelimab groups versus -29.4% for placebo (P<0.001) at week 16. Sustained clinical responses and reductions in inflammatory biomarkers were noted during 24 weeks of treatment and up to 32 weeks after drug withdrawal. This demonstrates that targeting this pathway has the potential for durable responses even after therapy has ended. No safety concerns were noted, with low rates of serious adverse events and similar rates of treatment-emergent adverse events compared to placebo.[9] Phase 3 trials are currently underway.

Rocatinlimab, which targets the OX40 receptor, has also been investigated in a phase 2 trial, with a robust phase 3 program currently ongoing.[10] In a double-blinded, placebo-controlled phase 2b trial, the efficacy and safety of rocatinlimab were evaluated in adults with moderate-to-severe AD. Patients received varying doses of rocatinlimab (150 mg or 600 mg every 4 weeks, or 300 mg or 600 mg every 2 weeks) or a placebo for 18 weeks. This initial treatment period was followed by an 18-week active-treatment extension and a 20-week off-treatment follow-up. The primary endpoint was met as all rocatinlimab dosing regimens significantly reduced EASI scores at week 16 compared to placebo. The most notable improvement was observed in the 300 mg every 2 weeks group (−61.1% versus −15.0% for placebo, P<0.0001). This study also showed

that rocatinlimab significantly improved patient-reported outcomes, including pruritus, sleep disturbance, and health-related quality of life, with benefits maintained for at least 20 weeks post-treatment.[12]

Targeting IL-22

IL-22 plays a key role in epidermal dysfunction and chronic inflammation by promoting epidermal hyperplasia and inhibiting skin barrier function. Consequently, it contributes to the chronic, lichenified lesions observed in AD. In a previous, double-blinded, phase 2a trial, the efficacy and safety of fezakinumab, an IL-22 monoclonal antibody, were evaluated in adults with moderate-to-severe AD.[13] The primary endpoint, which was the change in the SCORing Atopic Dermatitis (SCORAD) score at week 12, was not met, as the difference between the fezakinumab and placebo groups was not statistically significant (mean decline: 13.8 versus 8.0; P=0.134). However, significant improvements were observed in the severe AD subset (SCORAD ≥50) at week 12 (mean decline: 21.6 versus 9.6; P=0.029).[13] Although further studies were not pursued, this trial identified IL-22 as a potential target.

Temtokibart is a novel monoclonal antibody that specifically targets the IL-22 receptor subunit alpha-1 (IL-22RA1) of the heterodimeric IL-22 receptor, blocking signalling of IL-22, IL-20, and IL-24 signalling through the IL-20 receptor, Type 2. In a phase 2a study (NCT04922021) temtokibart was evaluated for its efficacy and safety. By week 16, temtokibart demonstrated significant improvements compared to placebo, with EASI-75 achieved by 51.7% of patients versus 24.1% in the placebo group, EASI-90 by 34.5% versus 10.3%, and EASI-100 by 20.7% versus 0%.[14] Further phase 3 studies are planned.

Other Targeted Pathways

Another approach of pathway-directed therapy has explored targeting the epithelial alarmin cytokines, including TSLP and IL-33. TSLP acts on Th2 cells to produce Th2 cytokines, such as IL-4, IL-5, IL-13, and IL-31, and directly stimulates sensory nerves to induce itch.[15] A randomized phase 2a clinical trial assessed the efficacy and safety of tezepelumab, a monoclonal antibody targeting TSLP that was previously approved for asthma, in adults with moderate-to-severe AD treated with TCS.[16] While tezepelumab showed numerical improvements over placebo in clinical endpoints such as EASI-50 (64.7% versus 48.2% at week 12, P=0.091) and pruritus reduction, these differences were not statistically significant.[16] Another alarmin cytokine that has been investigated is IL-33. A phase 2 randomized controlled trial investigated astegolimab, an anti-IL 33 receptor monoclonal antibody, in patients with moderate-to-severe AD.[17] The study did not show a statistically significant improvement in the primary endpoint, the percent change in EASI score from baseline to week 16 compared to placebo (-51.47% versus -58.24%, P=0.56).[17] In an unpublished phase 2 trial, with results posted on **ClinicalTrials.gov** (NCT03533751), etokimab, a monoclonal antibody targeting the IL-33 cytokine, was evaluated across four dosing groups. However, the trial did not demonstrate a significant difference from placebo in either primary or secondary outcomes.[18] The lack of success in targeting these single upstream cytokines or their pathways highlights the complexity of AD immunopathogenesis and the diverse inflammatory signalling involved in this chronic condition. However, problems with the study design of these proof-of-concept trials cannot be ruled out. Currently, a high-affinity, high-potency anti-TSLP monoclonal antibody, bosakitug, is being investigated in a phase 2 trial as monotherapy and in combination with dupilumab. The results are eagerly awaited to help determine the value of targeting an upstream alarmin.[19]

Challenges and Future Directions

AD is a complex heterogeneous inflammatory condition. Many patients do not respond adequately to, or have safety or tolerability issues with, current therapies. Therefore, there is an unmet need to explore new targets in the immunopathogenesis of AD to address this therapeutic gap. Multiple agents are currently in various phases of development, including IL-4/-13, IL-22, IL-31, TSLP, and OX40-OX40L inhibitors. Some of these, such as lebrikizumab and nemolizumab, have already received approval in some regions. Other agents are close to completing their phase 3 programs, including amlitelimab and rocatinlimab, and will likely be the next candidates for approval. Furthermore,

antibodies targeting the same cytokines but engineered with YTE technology—Fc modifications that enhance neonatal Fc receptor (FcRn) binding to prolong their half-life—are also in development to support less frequent dosing. APG777 and IMG007 are examples of such antibodies, with a YTE modification targeting IL-13 and OX40, respectively. Both are currently undergoing phase 2 studies in AD.[20]

Ongoing challenges in developing and approving targeted antibodies include long-term safety concerns with chronic immunomodulation, regulatory and reimbursement hurdles, and the need for predictive tools such as biomarkers to determine which therapy would be best for each patient. Despite these challenges, the development of biologic therapies to date has transformed the therapeutic landscape of AD management. This advancement has been driven by our better understanding of the immunopathogenesis of AD. With continuous innovation, the future of AD management offers renewed hope for disease control and an improved quality of life for patients worldwide.

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Financial Disclosures

M.G.: Investigator, speaker and/or adviser: AbbVie, Acelyrin, Alumis, Amgen, Akros, Arcutis, Aristea, AnaptysBio, Apogee, Bausch Health, BMS, Boehringer Ingelheim, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, Inmagene, JAMP Pharma, Janssen, LEO Pharma, L'Oreal, MedImmune, Meiji, Moonlake, Nektar, Nimbus, Novartis, Organon, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, Tarsus, Takeda, UCB, Union, Ventyx and Vyne.

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