

Biologics for Atopic Dermatitis



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KEYWORDS

• Atopic dermatitis • Biologics • Dupilumab • Immune dysregulation • Lebrikizumab
• Nemolizumab • Omalizumab • Tralokinumab

KEY POINTS

- The pathophysiology of atopic dermatitis includes both skin barrier and immune abnormalities, with type 2 immune deviation central to several clinical phenotypes and underlying endotypes.
- Recognition of the persistent nature and systemic aspects of atopic dermatitis provides a rationale for treatment with a biologic.
- Dupilumab, a biologic that targets type 2 immunity by blocking interleukin (IL)-4 and IL-13 binding to IL-4 receptor alpha, has been approved for patients 6 years of age and older with moderate to severe atopic dermatitis.
- Monoclonal antibodies targeting IL-13 and IL-31 receptor A are in phase 3 trials, whereas other targets include IL-33, thymic stromal lymphopoietin, OX40, and IL-22 and may become part of a precision medicine approach to atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that has become a global health problem.^{1,2} The Global Burden of Disease Study showed that dermatitis, including AD, was the leading skin disease in terms of global burden of disease measured by disability-adjusted life years.³ Epidemiologic studies in the United States have shown prevalence of up to 18% in school-aged children⁴ and 7% in adults responding in the Atopic Dermatitis in America survey.⁵ In this survey, 29% were classified as having moderate disease and 11% as having severe disease. As a chronic, relapsing pruritic disease, AD has a profound impact on the quality of life of patients and families.⁶ In a study of adults with moderate to severe AD, 85% reported problems with itch frequency, 41.5% reported itching greater than or equal to 18 h/d, 55% reported AD-related sleep disturbance greater than or equal to 5 d/wk, and 21.8% reported clinically relevant anxiety or depression.⁷ Atopic comorbidities of AD, including asthma and allergies, are well recognized, although identifying patients at increased risk for an atopic march remains problematic.⁸ Nonatopic comorbidities, including neuropsychiatric and cardiovascular disorders, are also being reported.^{9–11}

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RATIONALE FOR BIOLOGIC THERAPY IN ATOPIC DERMATITIS

Historically, AD has been thought of as predominantly a disease of children, often outgrown and treated with topical antiinflammatory therapy in a reactive manner. In fact, AD remains a persistent disease or has new onset in a significant number of adults.^{12,13} The pathophysiology of AD is complex and characterized by skin barrier abnormalities and immune dysregulation.¹⁴ The systemic nature of AD has become increasingly recognized with inflammatory changes that can be measured in a blood proteomic signature at an early age.¹⁵ Recent studies point to systemic T-cell activation with expansion of circulating T-helper (Th) 2 and Th22 cells.¹⁶ Furthermore, non-lesional AD skin is characterized by broad terminal differentiation defects in addition to immune abnormalities.¹⁷ Although several clinical phenotypes and endotypes have been described, type 2 immunity seems to be central to all of them (Fig. 1).¹⁸ Type 2 immune deviation seems to define a distinct AD phenotype and endotype characterized by more severe disease, with *Staphylococcus aureus* colonization, greater allergen sensitization, and barrier dysfunction.¹⁹ The dysbiosis of the skin microbiome in patients with AD has been shown to be related to altered epidermal lipids secondary to type 2 cytokine dysregulation.²⁰ Recognition of the systemic nature of AD has important translational implications providing a rationale for systemic treatments, especially those targeting type 2 immunity. Of note, advances in the understanding of disease mechanisms have serendipitously coincided with technological advances, ushering in a new era of targeted therapy for AD.¹ This article discusses the use of biologics in patients with AD.

WHICH PATIENTS WITH ATOPIC DERMATITIS WARRANT THERAPY WITH A BIOLOGIC?

Identifying appropriate patients with AD for treatment with systemic therapy, including biologics, has been discussed in several publications.^{21–24} A multidisciplinary expert

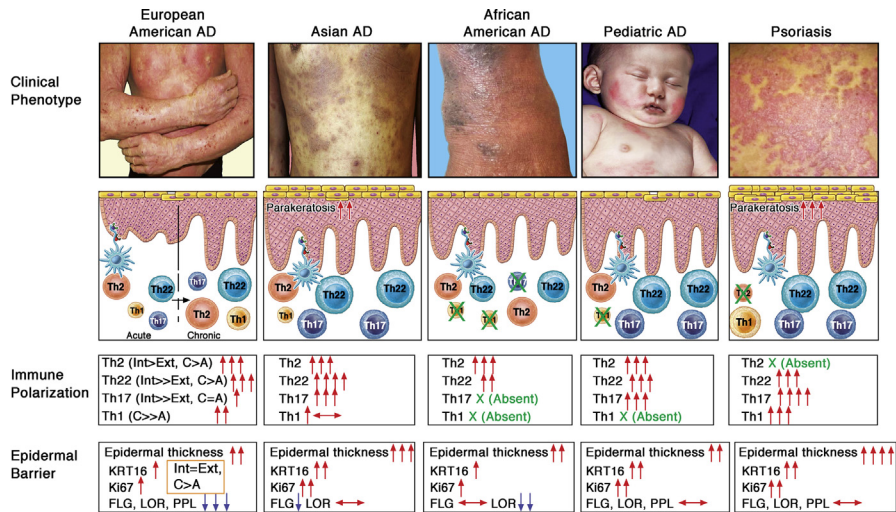


Fig. 1. AD clinical phenotypes and related endotypes. Ext, external; Int, internal. (From Czar-nowicki T, He H, Krueger JG, et al. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143:1-11; with permission.)

perspective provided a Delphi approach to addressing several key questions, including defining moderate to severe AD as well as treatment failure and recommended a biologic (dupilumab) as a first-line systemic treatment option.²¹ The International Eczema Council provided an algorithm for evaluating patients with AD when considering them for systemic therapy,²² the AD Yardstick added a biologic (dupilumab) to the stepwise management of AD,²³ and a more recent review on managing severe AD included an annotated figure addressing both evaluation and treatment, including with a biologic.²⁴

HISTORICAL PERSPECTIVE ON BIOTHERAPEUTICS IN ATOPIC DERMATITIS

Biotherapeutic trials in AD have included treatment with high-dose intravenous immunoglobulin (IVIG), shown to have immunomodulatory effects in AD. IVIG contains high concentrations of staphylococcal toxin-specific antibodies that can inhibit in vitro activation of T cells by staphylococcal toxins.²⁵ IVIG has also been shown to reduce interleukin (IL)-4 expression in AD.²⁶ However, treatment of AD with IVIG has yielded conflicting results, with studies that have not been controlled and have involved small numbers of patients and a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review of systemic therapies found that IVIG was not efficacious in the treatment of moderate to severe AD.²⁷

Interferon (IFN)-gamma suppresses immunoglobulin (Ig) E synthesis and inhibits Th2 cell function and treatment of patients with moderate to severe AD with subcutaneous recombinant human IFN- γ (rhIFN- γ), a biologic response modifier that resulted in reduced clinical severity and decreased total circulating eosinophil counts.^{28,29} Long-term open-label studies with 50 $\mu\text{g}/\text{m}^2$ rhIFN- γ given daily or every other day also showed clinical benefit.^{30,31} Effective dosing with rhIFN- γ was associated with a decrease in eosinophil counts, suggesting that a subset of patients treated with rhIFN- γ would respond to individualized titration of their treatment dose.³² Recombinant human IFN- γ has also been used to treat pediatric patients with AD complicated by eczema herpeticum.³³ However, rhIFN- γ -1b is currently not US Food and Drug Administration (FDA) approved for AD.

The observation that patients with AD often have increased circulating eosinophil counts and that products of eosinophil degranulation can be found in their dermis would provide a rationale for targeting IL-5, a cytokine essential for eosinophil growth, differentiation, and migration. However, treatment with mepolizumab, a monoclonal antibody to human IL-5, failed to show efficacy in patients with moderate to severe AD.³⁴ A limitation of this study was that patients were treated with only 2 doses of mepolizumab over a 2-week period, a regimen that may not have adequately assessed this biologic's effect. Mepolizumab was subsequently studied for a longer treatment period but again did not meet its primary end points despite reducing circulating eosinophil counts.³⁵

Rituximab, a chimeric monoclonal anti-CD20 antibody, was shown to be beneficial in a small open trial of patients with severe AD who received 2 doses of 1000 mg by intravenous infusion 2 weeks apart.³⁶ Histology of skin biopsies showed significant improvement in spongiosis, acanthosis, and dermal cell infiltrates. Expression of IL-5 and IL-13 was also reduced after therapy. Although total serum IgE levels were reduced, allergen-specific IgE levels were not affected. In contrast, treatment with rituximab 500 mg intravenously given twice over a 2-week interval to 2 patients with severe AD resulted in only a transient improvement in clinical scores followed by deterioration.³⁷ In a novel approach, a small group of patients with severe refractory AD received either rituximab followed by omalizumab or omalizumab followed by

rituximab, with positive outcomes suggesting that optimal therapy may require combinations of biologics in select patients, although this would ideally be driven by better understanding the underlying disease mechanisms.³⁸

CURRENTLY APPROVED BIOLOGIC

Dupilumab is a fully human monoclonal antibody directed at the IL-4 receptor alpha (IL-4R α), thus interfering with signaling by both IL-4 and IL-13, 2 key type 2 cytokines (Fig. 2).³⁹ IL-4 binds to type I receptors composed of IL-4R α - γ c heterodimers expressed on hematopoietic cells, whereas both IL-4 and IL-13 can bind to type II receptors composed of IL-4R α -IL-13R α 1 complexes expressed on both hematopoietic and nonhematopoietic cells. Treatment of patients with AD with dupilumab was shown to suppress molecular markers of cutaneous and systemic type 2 inflammation, as well as reverse epidermal abnormalities that coincided with clinical improvement.⁴⁰ In 2 phase 3 trials (LIBERTY AD SOLO 1 and 2), adult patients with moderate to severe AD inadequately controlled on topical treatment were treated with dupilumab, 600-mg loading dose followed by 300 mg weekly or every other week or placebo by subcutaneous injection.⁴¹ The primary outcome of an Investigator's Global Assessment (IGA) of 0 or 1 (clear or almost clear) and a reduction of 2 points or more in that score from baseline at week 16 was achieved by 36% to 38% of patients on dupilumab monotherapy at week 16 versus 8% to 10% on placebo ($P < .001$). In addition, improvement of at least 75% in Eczema Area and Severity Index (EASI-75) from baseline to week 16 was reported in ~50% of patients on dupilumab. Several other clinically relevant outcome measures, including pruritus scores and patient-reported outcome measures, were also significantly improved in the patients treated with the biologic.

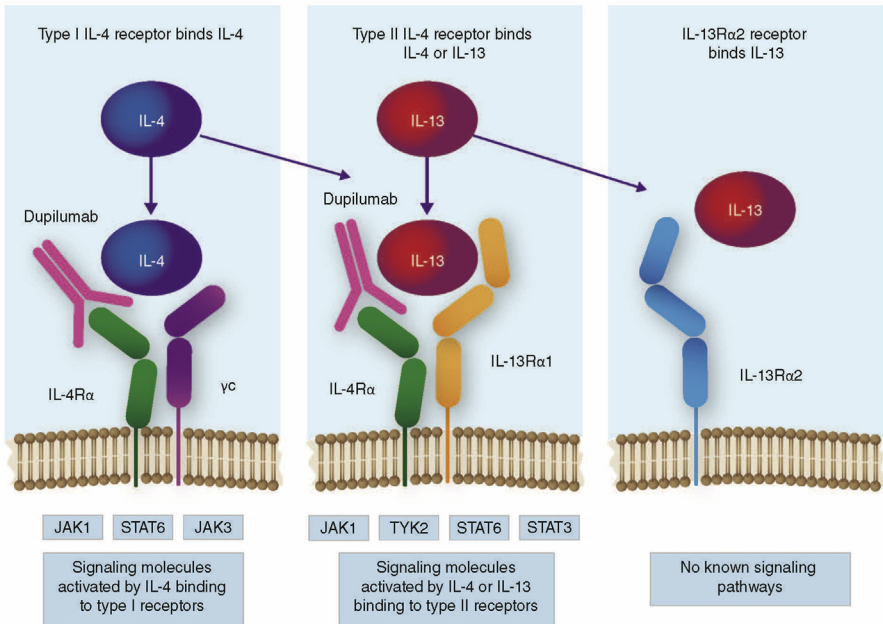


Fig. 2. Type I and type II IL-4 receptors. (From Hamilton JD, Ungar B, Guttman-Yassky E. Drug evaluation review: dupilumab in atopic dermatitis. *Immunotherapy*. 2015;7(10):1043-58; with permission.)

Of note, median disease duration in patients enrolled in the phase 3 trials was ~26 years, median affected body surface area was greater than 50%, and median EASI ~30 (≥ 21.1 = severe AD). In addition, ~33% of patients had received systemic corticosteroids and ~30% had been treated with systemic immunosuppressives. A critical clinical concept that was not immediately appreciated was that a significant number of patients treated with dupilumab who did not achieve the primary end point of IGA 0 or 1 (clear or almost clear) still had marked improvement as assessed by both investigator-reported and patient-reported validated measures compared with placebo: EASI (-48.9% vs -11.3% , $P < .001$), pruritus Numerical Rating Scale (NRS) (-35.2% vs -9.1% , $P < .001$), affected Body Surface Area (BSA) (-23.1% vs -4.5% , $P < .001$), Patient Oriented Eczema Measure (POEM) score greater than or equal to 4-point improvement (57.4% vs 21.0% , $P < .001$), and Dermatology Life Quality Index score greater than or equal to 4-point improvement (59.3% vs 24.4% , $P < .001$).⁴² A 52-week study with dupilumab used together with topical steroids (LIBERTY AD CHRONOS) reproduced both the efficacy and safety of the monotherapy trials, showing sustained benefit over an extended period of time.⁴³ An additional trial in adults with AD with inadequate response to or intolerance of Cyclosporine A (CsA), or for whom CsA treatment was medically inadvisable (LIBERTY AD CAFÉ), also provided similar efficacy and safety data.⁴⁴

Injection-site reactions and conjunctivitis were more frequent in the dupilumab-treated patients than in the placebo groups. Although the conjunctivitis has not been fully explained, it was for the most part self-limited, and only 1 patient in the phase 3 monotherapy trials discontinued study treatment.⁴¹ A recent review of randomized placebo-controlled trials of dupilumab in AD ($n = 2629$), asthma ($n = 2876$), chronic rhinosinusitis with nasal polyps (CRSwNP) ($n = 60$), and eosinophilic esophagitis (EoE) ($n = 47$) found that the incidence of conjunctivitis was greater with dupilumab treatment in most AD trials but very low and similar to that seen in placebo-treated patients in the asthma, CRSwNP, and EoE trials.⁴⁵ Greater baseline AD disease severity and history of prior conjunctivitis were associated with increased conjunctivitis incidence. Of note, conjunctivitis was mostly mild to moderate in severity, and most cases recovered or resolved while continuing on dupilumab. Common treatments included ophthalmic corticosteroids, antibiotics, and antihistamines or mast cell stabilizers. Several studies aim to address the underlying pathomechanisms of conjunctivitis in patients with AD treated with dupilumab, including the role of goblet cells (NCT04276623) and cytokine profile of tears (NCT04066998).

As with any new systemic therapy, dupilumab trials were monitored for any signals of increased infections, although the mechanism of action targeting type 2 immunity suggested the potential to correct both immune and epidermal abnormalities.⁴⁰ Data from the large phase 3 trials were reassuring, but reflected only 16 weeks of exposure.⁴¹ The 52-week trial provided further reassurance to clinicians,⁴³ and ongoing long-term open extension studies continue to add to the safety profile of this biologic.⁴⁶ In a randomized, double-blinded, placebo-controlled study in adults with AD, dupilumab was shown not to adversely affect antibody responses to vaccines (Tdap and quadrivalent meningococcal polysaccharide).⁴⁷ Recently published data from a blinded, placebo-controlled trial showed that patients treated with dupilumab had decreased *S aureus* colonization and increased microbial diversity that correlated with clinical improvement of AD and biomarkers of type 2 immunity.⁴⁸ In addition, in an analysis of pooled data from 7 randomized, placebo-controlled dupilumab trials in 2932 adults with moderate to severe AD, serious infections were reduced with dupilumab, as were bacterial and other nonherpetic skin infections.⁴⁹ Although

herpesviral infection rates overall were slightly higher with dupilumab than placebo, clinically important herpesviral infections (eczema herpeticum, herpes zoster) were less common with dupilumab. Systemic antiinfective medication use was lower in dupilumab-treated patients.

Subsequently, a randomized, double-blind, parallel-group, phase 3 clinical trial (LIBERTY AD ADOL) was conducted in the United States and Canada in 251 adolescent patients aged 12 to 17 years with moderate to severe AD.⁵⁰ In this monotherapy trial, patients were stratified by severity and body weight to 16 weeks of treatment with 1 of 4 regimens: dupilumab 400-mg loading dose, then 200 mg every 2 weeks (baseline weight <60 kg); dupilumab 600-mg loading dose, then 300 mg (baseline weight $\geq$ 60 kg) every 2 weeks; dupilumab 600-mg loading dose, then 300 mg every 4 weeks; or placebo with all patients receiving injections every 2 weeks to maintain study blinding. A significantly higher proportion of patients treated with both dupilumab regimens achieved EASI-75 and IGA 0 or 1 at week 16 versus placebo-treated patients. Efficacy of the every-2-weeks regimen was generally superior to the every-4-weeks regimen. The incidence of conjunctivitis in the dupilumab-treated patients ($\sim$ 10%) was similar to that seen in the adult trials. A poshoc subgroup analysis was performed on patients whose IGA was greater than 1 at week 16.⁵¹ Of that subgroup, 80.5% of patients receiving dupilumab every 2 weeks versus 23.5% on placebo experienced clinically meaningful improvements in AD signs, symptoms, or quality of life at week 16. Clinically meaningful improvement in 1 or more of 3 domains of signs, symptoms, and quality of life was defined as an improvement of greater than or equal to 50% in EASI, greater than or equal to 3 points in Peak Pruritus Numerical Rating Scale, or greater than or equal to 6 points in the Children's Dermatology Life Quality Index from baseline. Similar to the adult experience,⁴² these data point to the limitations of using IGA as a primary outcome in AD. On May 26, 2020 the FDA approved dupilumab in children 6–11 years with moderate-to-severe atopic dermatitis with weight based dosing by subcutaneous injection: 15 to < 30 kg, 600 mg initial dose, then 300 mg Q4weeks; 30 to <60kg, 400 mg initial dose, then 200 mg Q 2wks; $\geq$ 60 kg, 600 mg initial dose, then 300 mg Q2 wks.⁵² A study of safety, pharmacokinetics, and efficacy of dupilumab in patients greater than or equal to 6 months old to less than 6 years old with severe AD (Liberty AD PRE-SCHOOL) is currently recruiting (NCT03346434). In addition, pediatric patients with AD have been treated with dupilumab prescribed off label.^{53,54}

Dupilumab is approved in the United States for patients aged greater than or equal to 12 years with moderate to severe AD uncontrolled by topical prescription medicines or when those medications are not advised. The approved dosing regimen in adults and in adolescents greater than or equal to 60 kg is a 600-mg loading dose subcutaneously followed by 300 mg subcutaneously every 2 weeks. In adolescents less than 60 kg, the dosing regimen is a 400-mg loading dose subcutaneously followed by 300 mg subcutaneously every 2 weeks. Injections can be self-administered at home, and patients do not require any laboratory monitoring or to be prescribed auto-injectable epinephrine. A study with dupilumab autoinjector has been completed and is under FDA review (NCT03050151). To date, treatment regimens with more or less frequent dosing or stopping and restarting treatment have not been formally studied. One study of patients who had dupilumab discontinued before restarting open-label therapy showed quick recapture of disease control and no adverse events.⁴⁶ However, patients could develop clinically relevant antidrug antibodies (ADAs) with repeated stopping and restarting a biologic, and 2 patients with hypersensitivity reactions on dupilumab in the phase 3 trials had high titers of ADA.⁴¹ Of note, patients with AD with comorbidities including asthma and rhinosinusitis seem to respond to treatment

with dupilumab as well as those without these concomitant diseases (manuscript submitted). Dupilumab is also being studied in combination with anti-IL-33 (REGN3500) (NCT03736967) as well as with apremilast, a systemic phosphodiesterase 4 inhibitor, as add-on therapy (NCT04306965).

OFF-LABEL USE OF BIOLOGIC FOR ATOPIC DERMATITIS

Omalizumab, a recombinant humanized monoclonal antibody that inhibits binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils, has been used in AD with variable results. Treatment of patients with AD with omalizumab off label has mainly been reported in case reports and case series, showing both clinical improvement and lack of benefit.⁵⁵ Specific markers have not been identified that would define responders. Adult patients with AD that responds to treatment have wild-type *FLG* mutations. A systematic review and meta-analysis of omalizumab in AD found that fewer than 50% of the patients treated with this biologic achieved a significant clinical improvement.⁵⁶ The 2 randomized controlled trials from that review failed to show significant clinical improvement with omalizumab or the response was comparable with that of the control group. However, the investigators suggested that, because 43% of patients treated with omalizumab had a good response, a subset of patients with AD, possibly those with an urticarial component to their disease, might still benefit from this therapy. Recently, a randomized clinical trial in children with severe AD found that omalizumab significantly reduced disease severity and topical steroid use.⁵⁷ As discussed earlier (rituximab), omalizumab may be used in the future as part of a combination or sequential therapy.³⁸ Of note, a phase 2 trial of ligelizumab (QGE031), a monoclonal antibody with greater affinity for IgE than omalizumab, was completed in 2013 with no results posted, suggesting lack of efficacy in AD (NCT01552629).

BIOLOGICS UNDERGOING EVALUATION IN ATOPIC DERMATITIS

IL-13 is a key type 2 cytokine involved in several pathogenic processes in AD, including skin barrier defects, inflammatory responses, pruritus, and dysbiosis.⁵⁸ IL-13 can bind to IL-13Rα1, which, together with IL-4Rα, forms a heterodimeric receptor complex, as well as to IL-13Rα2, thought to function as a decoy receptor that may be involved in endogenous IL-13 regulation (see Fig. 2).⁵⁹ Monoclonal antibodies targeting IL-13 interfere with IL-13 binding to IL-13Rα1, IL-4Rα, and/or IL-13Rα2. Tralokinumab is a human recombinant IgG4 monoclonal antibody that prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2. Tralokinumab was studied in a phase 2b, randomized, double-blinded, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of 3 doses of tralokinumab administered by subcutaneous injection in adults with moderate to severe AD every 2 weeks for 12 weeks together with concomitant topical steroids (NCT02347176).⁶⁰ At week 12, compared with placebo, tralokinumab 300 mg significantly improved change from baseline in EASI, and a greater percentage of participants achieved an IGA of 0 or 1 and reduction of greater than or equal to 2 grades from baseline (26.7% vs 11.8%). Of note, clinical improvement was greater in patients who had increased biomarkers (Dipeptidyl peptidase-4 (DPP-4) and periostin) associated with increased IL-13 activity. Patients treated with tralokinumab 300 mg showed improvements in SCORAD (Scoring Atopic Dermatitis), Dermatology Life Quality Index, and pruritus numeric rating scale scores versus placebo. Upper respiratory tract infections were the most frequent treatment-emergent adverse events reported as related to study drug in the placebo (3.9%) and pooled tralokinumab (3.9%) groups, with frequency of conjunctivitis 5.9% in tralokinumab

150 mg group and 3.9% in placebo group. This study was confounded by small numbers of patients in each of the 4 treatment regimens and the high placebo response with concomitant topical corticosteroid use. Phase 3 monotherapy trials (ECZTRA 1, NCT03131648, and ECZTRA 2, NCT03160885) for up to 52 weeks in patients 18 years of age or older with moderate to severe AD who are candidates for systemic therapy have been completed, with results pending. In a separate trial, immune responses to Tdap and meningococcal vaccines in patients treated with tralokinumab versus placebo will be assessed (NCT03562377).

Lebrikizumab is another monoclonal antibody targeting IL-13 that selectively prevents formation of the IL-13R α 1/IL-4R α heterodimer receptor signaling complex. Because its binding is distinct from that of tralokinumab,⁶¹ both monoclonal antibodies targeting IL-13 could be expected to have distinct efficacy and safety profiles. In a double-blind, phase 2 study, adults with moderate to severe AD were randomized 1:1:1:1 to lebrikizumab 125 mg single dose, lebrikizumab 250 mg single dose, lebrikizumab 125 mg every 4 weeks for 12 weeks, or placebo every 4 weeks for 12 weeks after a 2-week topical steroid run-in (NCT02340234).⁶² At week 12, significantly more patients achieved the primary end point of EASI-50 with lebrikizumab 125 mg every 4 weeks (82.4%) than placebo every 4 weeks (62.3%), and adverse events were similar between groups and mostly mild or moderate. Again, the study design with mandated topical steroid use limited a proper evaluation of lebrikizumab. Subsequently, lebrikizumab was trialed as a monotherapy using a loading dose protocol in a phase 2b monotherapy trial of patients 18 years of age or older with moderate to severe AD randomized 2:3:3:3 to placebo every 2 weeks or to subcutaneous lebrikizumab 125 mg every 4 weeks after a 250-mg loading dose, 250 mg every 4 weeks after a 500-mg loading dose, or 250 mg every 2 weeks after a 500-mg loading dose at baseline and week 2 (NCT03443024).⁶³ The primary end point was the percentage change in EASI from baseline to week 16 and, compared with placebo, all of the lebrikizumab groups showed dose-dependent, statistically significant improvement: 125 mg every 4 weeks (−62.3%), 250 mg every 4 weeks (−69.2%), and 250 mg every 2 weeks (−72.1%). Treatment-emergent adverse events were reported in placebo patients (46.2%) and in lebrikizumab groups (48.8%–61.3%), with most reported as mild to moderate that did not require discontinuation. Conjunctivitis was reported in 2.6% of patients treated with lebrikizumab. Lebrikizumab is currently being evaluated in 2 phase 3 trials in patients 12 years of age and older with moderate to severe AD, including a 52-week randomized, double-blind, placebo-controlled, parallel-group study to confirm the safety and efficacy of lebrikizumab as monotherapy for treatment of moderate to severe AD using a 16-week induction treatment period and a 36-week long-term maintenance treatment period using both every-2-weeks and every-4-weeks dosing regimens (NCT04178967) and a 52-week randomized, double-blind, placebo-controlled, parallel-group study to confirm the safety and efficacy of lebrikizumab as monotherapy for treatment of moderate to severe AD using a 16-week induction treatment period and a 36-week long-term maintenance treatment period (NCT04146363). Head-to-head trials of anti-IL-13 biologics versus dupilumab may be needed to answer the question of whether targeting IL-13 alone or both IL-4 and IL-13 is necessary to effectively block type 2 inflammation.⁶⁴

IL-31 is a pruritus-inducing type 2 cytokine that is upregulated in AD, with IL-31 receptor A (IL-31RA) detected in keratinocytes and nerve fibers in the dermis of AD and in the neurons of normal dorsal root ganglia.^{65,66} Nemolizumab, a humanized anti-IL-31RA monoclonal antibody, binds to IL-31RA and inhibits IL-31 signaling. In a phase 2, randomized, double-blind, placebo-controlled 12-week trial, adults with moderate to

severe AD inadequately controlled by topical treatments were treated with subcutaneous nemolizumab dosed by body weight (0.1 mg, 0.5 mg, or 2.0 mg/kg) or placebo every 4 weeks as well as an exploratory dose of 2.0 mg/kg of nemolizumab every 8 weeks.⁶⁷ The primary end point was the percentage improvement from baseline in pruritus visual analog scale (VAS) score at week 12. Treatment with nemolizumab every 4 weeks resulted in changes on the pruritus VAS of −43.7% in the 0.1-mg group, −59.8% in the 0.5-mg group, and −63.1% in the 2.0-mg group versus −20.9% in the placebo group. Improvement in the EASI was −23.0%, −42.3%, and −40.9%, respectively, in the nemolizumab groups versus −26.6% in the placebo group. Changes in BSA involved were −7.5%, −20.0%, and −19.4% with nemolizumab versus −15.7% with placebo. Treatment discontinuation was similar across the 3 dosing regimens of nemolizumab given every 4 weeks and placebo. Although this trial was not designed to definitively compare responses between the dosing regimens, the largest reduction in pruritus at week 12 occurred in the group treated with nemolizumab 0.5 mg/kg every 4 weeks. It is unclear why the higher dose of nemolizumab did not result in incremental benefit. In addition, although the investigators stated that limited size and length of the trial precluded them from making any conclusions regarding adverse events, a review of the data shows that a small percentage of patients treated with nemolizumab developed peripheral edema, pointing to the difficulty in predicting rare adverse events with novel biologic therapies. In a 52-week, double-blind extension study, improvement from baseline in pruritus VAS score was maintained or increased from weeks 12 to 64, with greatest improvement in the 0.5 mg/kg every 4 weeks group with no new safety concerns identified (NCT01986933).⁶⁸ Using a different approach, Silverberg and colleagues⁶⁹ treated patients with moderate to severe AD and severe pruritus with nemolizumab dosed with either 10, 30, or 90 mg by subcutaneous injections every 4 weeks after a loading dose versus placebo and allowed the use of topical corticosteroids in a 24-week, randomized, double-blind, multicenter study (NCT03100344). When used in combination with topical steroids, nemolizumab improved EASI, immunoglobulin, and/or NRS-itch scores, with the 30-mg dose being most effective. There was a low incidence of peripheral edema observed in both placebo-treated and nemolizumab-treated patients with no serious cases and 2 subjects treated with nemolizumab discontinued early because of increased creatine kinase levels. A dose-dependent increase in asthma events in patients with preexisting asthma was reported, with mostly mild and very few moderate events that were manageable and reversible. Of note, patients with moderate to severe prurigo nodularis and severe pruritus treated with nemolizumab reported gastrointestinal symptoms, including abdominal pain and diarrhea, as well as musculoskeletal symptoms (NCT03181503).⁷⁰ Phase 3 studies currently underway may shed further light on the role of IL-31 in AD as well as rare adverse events (NCT03989349, NCT03985943, NCT03989206). Because targeting of IL-4 and IL-13 also results in decreased pruritus,^{41,60,63} head-to-head trials may further elucidate optimal positioning of emerging biologics in AD.

Tezepelumab, a monoclonal antibody, targets thymic stromal lymphopoietin (TSLP), a cytokine that is implicated in the pathogenesis of AD.¹⁴ Epidermal barrier perturbation results in keratinocyte release of several chemokines and cytokines, including TSLP, which in turn acts on group 2 innate lymphoid cells, Th2 cells, and dendritic cells, promoting a type 2 inflammatory milieu, and also directly on cutaneous sensory neurons, contributing to pruritus. Thus, targeting TSLP, which has been called a master switch for allergic inflammation, seems to be strategically important in the present understanding of AD. However, a phase 2a trial of tezepelumab 280 mg or placebo every 2 weeks plus class 3 topical corticosteroids did not achieve statistical

significance in EASI-50 at week 12, the primary end point (NCT02525094).⁷¹ Greater-than-expected response rates in placebo-treated patients were likely attributable to topical steroid use. A dose-ranging trial of tezepelumab as monotherapy for AD is currently recruiting and may yield better results (NCT03809663). Although proof-of-concept results from a small study suggested potential benefit of targeting a different alarmin cytokine IL-33,⁷² etokimab (ANB020), an anti-IL-33 monoclonal antibody failed to meet its primary end point in a phase 2b trial in AD (NCT03533751). A different biologic targeting IL-33 (REGN3500) is also being investigated as a monotherapy and in combination with dupilumab (as discussed earlier) (NCT03736967). Inhibiting OX40-OX40 ligand interaction could disrupt TSLP-driven type 2 inflammation and a proof-of-concept trial of GBR 830, a humanized anti-OX40 monoclonal antibody, showed improvement in gene signatures and clinical scores.⁷³ Of note, 2 intravenous doses of the drug administered 4 weeks apart induced significant improvement of tissue and clinical measurements even 42 days after the last dose, suggesting disease-modifying potential.

The Th22 pathway has been shown to be important in AD, with IL-22 participating in epidermal disorder (see [Fig. 1](#)).⁷⁴ By attenuating keratinocyte terminal differentiation and inhibiting tight-junction formation, IL-22 can contribute to barrier dysfunction, and this cytokine's levels are significantly increased in lesional AD skin, correlating with disease severity. A phase 2a clinical trial of fezakinumab, an anti-IL-22 monoclonal antibody, showed significant clinical improvements versus placebo in patients with severe AD (SCORAD > 50), but not in patients with moderate AD.⁷⁵ A study of fezakinumab that focused on mechanistic responses showed reversal of multiple pathologic features in AD skin biopsies, as well as reduced overall inflammatory burden, not just in the Th22 pathway but also affecting Th1-related, Th2-related, and Th17-related markers.⁷⁶ Treatment effects were observed primarily in patients with high baseline IL-22 levels, and, interestingly, participants with low baseline levels of IL-22 had a tendency toward exacerbation of their AD.

SUMMARY

AD is a common inflammatory skin disease that is often persistent and can have recurrence or new onset in adults. Pathophysiology is complex, with both skin barrier and immune abnormalities, including systemic aspects with type 2 immunity central to several clinical phenotypes and endotypes. Dupilumab, a biologic targeting IL-4 and IL-13, seems to correct both cutaneous and systemic abnormalities and has been approved for patients greater than or equal to 6 years with moderate to severe AD. Biologics currently in trials for AD include those targeting IL-13, IL-31RA, TSLP, IL-33, OX40, and IL-22. Further insights into disease mechanisms will help clinicians make more informed therapeutic recommendations as they evolve in the goal to provide precision medicine.

CLINICAL CARE POINTS

- In evaluating whether a patient with AD is a candidate for systemic therapy, define the severity of the patient's AD; review current therapy; and consider alternative diagnoses, as well as concomitant infections, role of stressors, and irritant, allergic, or microbial triggers.
- Before starting a patient on dupilumab, provide education about the chronic, relapsing nature of AD, document severity of the patient's disease, including body surface area involved, and review potential adverse events to be aware of.

- Patients with AD on a biologic may still require treatment with a topical antiinflammatory therapy.

CONFLICT OF INTEREST

M. Boguniewicz has served as a consultant for Regeneron and Sanofi-Genzyme.

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