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Biologics for Treatment of Atopic Dermatitis: Current Status and Future Prospect

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Abstract

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by intense pruritus and recurrent eczematous lesions which significantly impair quality of life. It is a heterogeneous disease affecting both children and adults. The treatment of moderate-to-severe forms of AD is challenging, as topical corticosteroids are often insufficient to achieve disease control or inappropriate, and off-label use of immunosuppressants may have significant undesirable side effects. The development of targeted biologic therapies specifically for AD is thus highly desirable. Dupilumab is the only biologic therapy FDA-approved for the treatment of moderate-to-severe AD in patients 6 years and older, with consistent long-term efficacy and safety trial data. In this article, we review the mechanisms, safety, and efficacy of dupilumab from recent clinical trials, and we review the current data, mechanism of action, clinical efficacy, and limitations of new biologics currently in phase 2 and 3 clinical trials (lebrikizumab, tralokinumab, nemolizumab, tezepelumab, and ISB 830).

Keywords

Atopic Dermatitis; Biologic therapy; Dupilumab; Eczema; GBR 830; ISB 830; Lebrikizumab; Nemolizumab; Tezepelumab; Tralokinumab

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Introduction

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases. Describing its incidence and prevalence is challenging due to substantial variation in diagnostic criteria used for its identification, fluctuating course, and geographical differences. The majority of cases starts in early childhood, but AD can have heterogeneous trajectory patterns, ranging from transient disease in early life, to relapsing remitting AD, chronic persistent AD, and long periods of remission followed by recurrence, or adult-onset AD.[1–3] While cumulative lifetime prevalence up to 30% has been reported, period prevalences are estimated to be 7-14% in children and 5-12% in adults.[1–3]

The clinical hallmarks of AD are eczematous lesions and intense itch. Many patients suffer from dry scaly skin and IgE-mediated sensitizations. Lesions can affect any part of the body, but typically show age-related morphology and distribution, with face, trunk, and extensor limb inflammatory involvement in infants and young children, and lichenified, chronic, dry flexural distribution in adults.[4]However, compared with childhood-onset AD, presentation of adult-onset AD is more heterogeneous, with more variation in lesional morphology and distribution, and greater predilection for the head, neck, hands, and feet.[5]

The pathophysiology of AD is complex and multifactorial, with strong genetic susceptibility, important contributions of immune dysregulation due to excessive T-helper(Th)2 and Th22 activity, with variable contributions of Th1/Th17, skin barrier dysfunction, and cutaneous dysbiosis (Figure 1).[6–10] Skin barrier dysfunction is characterized by downregulation of epidermal barrier proteins, including filaggrin, keratins, locrin, involucrin, and cell adhesion molecules, a disturbed intercellular lipid composition, and an altered composition of the skin microbiome, which together lead to increased permeability and proinflammatory signaling. Cutaneous inflammation is characterized by upregulated type 2 cytokines, such as interleukin(IL)-4, IL-13, and IL-31, heightening sensitization to allergens, risk of food allergy, airway hyperreactivity, and contributing to skin barrier dysfunction.[11–14]

“The Th22 pathway has also been shown to be involved in AD, with IL-22 participating in epidermal disorders. By attenuating keratinocyte terminal differentiation and inhibiting tight-junction formation, IL-22 is thought to contribute to barrier dysfunction.”[15] However, there is increasing evidence that AD is not dominated by one disease spectrum, but rather involves multiple alternating immune pathways comprised by several endotypes.[9, 17–19] Several subtypes, such as intrinsic, Asian, pediatric, and filaggrin-positive AD subcategories were shown to have differential upregulation in Th17/Th22 or Th1 axes. Thus, Th1 and Th17/Th22 modulation in addition to Th2 might provide broader and/or more sustained therapeutic benefit.[10]

AD is associated with numerous atopic comorbidities, including asthma, allergic rhinitis, food allergy, and eosinophilic esophagitis.[20] Increasing evidence supports the association of AD with other systemic inflammatory diseases, including alopecia areata, vitiligo, rheumatoid arthritis, and inflammatory bowel disease,[21–25] although well powered longitudinal studies are needed to confirm causal links. A systematic review of 74 studies

found no significant overall association between AD and allergic contact dermatitis (ACD), and in children referred for patch testing, ACD was more common in those without AD.[26, 27] It was also shown that ACD in the setting of AD has attenuated responses.[28] Furthermore, patients with AD have increased risk of psychiatric conditions, including attention-deficit hyperactivity disorder, anxiety, and depression.[20, 29]

The aim of AD management is to improve symptoms and achieve long-term eczema control with a multistep approach tailored according to disease severity (Figure 2). For all patients, basic management consists of continuous epidermal barrier repair with emollients and avoidance of individual triggers. Oral antihistamines are not recommended, as little evidence supports that they are effective for AD signs and symptoms, including pruritis.[4]

In moderate-to-severe AD, topical corticosteroids are the mainstay of treatment. However, patients with more severe AD often require treatment with systemic anti-inflammatory drugs, which may lead to significant side effects and hence treatment cessation, and efficacy is also moderate. Therefore, targeted biologics, large proteins which are injected and do not penetrate the lipid bilayer cell membrane, involving pathways directly responsible for AD are an attractive treatment. Dupilumab is the only biologic approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for moderate-to-severe AD.[30, 31] While dupilumab shows good efficacy, only approximately one-third of patients have complete clearance.[32] There is thus a large need for further innovative therapeutics, including other biologics selectively targeting cytokines involved in the inflammatory pathway of AD.[9]

The purpose of this review is to discuss the mechanisms, safety, and efficacy of biologics recently approved and currently in phase 2 and 3 clinical trials for treatment of moderate-to-severe AD (Table 1). In addition to biologics, other various targeted therapies, including JAK inhibitors and phosphodiesterase 4 inhibitors, are also in the pipeline for AD treatment at different stages of clinical trial.

Dupilumab

Dupilumab is a human IgG4κ monoclonal antibody (mAb) blocking IL-4 receptor (IL-4Rα), a shared receptor for IL-4 and IL-13,[33] key cytokines in Th2-mediated inflammation playing major roles in AD pathogenesis. Dupilumab was first approved by the FDA in 2017 and EMA in 2019 for use in moderate-to-severe AD in adults and adolescents (≥12 years) and recently approved in pediatric patients ages 6-11 years.[30, 31, 34] In 2018, dupilumab was approved in the USA and Europe as add-on maintenance treatment in patients with moderate-to-severe asthma with eosinophilic phenotype or oral corticosteroid-dependent asthma,[31, 35] and was approved in 2019 for chronic rhinosinusitis with nasal polyposis[36]. Beneficial effects of dupilumab were also reported in patients with eosinophilic esophagitis.[37]

Efficacy and safety of dupilumab for treatment of AD has been studied in several phase 3 clinical trials, including SOLO-1, SOLO-2,[32] LIBERTY AD CHRONOS,[38] and AD-1526.[39] In SOLO-1 and SOLO-2, dupilumab was used as monotherapy in adults with

moderate-to-severe AD inadequately controlled on topical therapies. Patients were randomized to two dupilumab arms and placebo, with a loading dose of 600 mg subcutaneously (SC) followed by 300 mg SC weekly, or a loading dose of 600 mg SC followed by 300 mg SC every other week, or placebo once weekly.[32]. Dupilumab achieved significant improvement in the primary endpoints, which was Investigator's Global Assessment (IGA) score of 0/1 and improvement of ≥2 points in IGA from baseline score at week 16. In SOLO-1, the primary outcome was achieved in 37% receiving weekly dupilumab and 38% receiving dupilumab every other week, vs. 10% on placebo (Figure 3A). Results from SOLO-2 were similar. Both SOLO-1 and SOLO-2 demonstrated a higher proportion of patients receiving dupilumab achieving EASI-75 vs. placebo (44%-52% dupilumab; 12%-15% placebo, Figure 3B). Reductions in pruritis and depression, as well as improved quality of life, also showed statistically significant differences vs placebo. In a pooled analysis, dupilumab significantly improved pruritus within 1-3 days of treatment initiation.[40]Dupilumab was overall well-tolerated, with conjunctivitis and injection site reactions reported at a higher rate in treatment groups vs. placebo.

The LIBERTY AD CHRONOS trial studied long-term safety and efficacy of dupilumab using similar dosing regimens to the SOLO trials, but on background topical corticosteroid (TCS) and for a period of 52 weeks.[38]. Similar to SOLO trials, the most frequent adverse events (AEs) were conjunctivitis and injection site reactions. The trial had 2 primary endpoints: IGA 0/1 and ≥2 points improvement from baseline, and EASI-75 improvement. At week 16, a higher proportion of patients receiving both dupilumab regimens significantly achieved primary outcomes vs. placebo (Figure 3A, 3B), with these efficacies maintained at week 52.

In the LIBERTY AD SOLO-CONTINUE trial, high-responding patients treated with dupilumab in SOLO were re-randomized to continue their original dupilumab regimen, 300mg SC weekly or every 2 weeks (q2w), 300mg SC every 4 weeks (q4w) or 8 weeks (q8w), or placebo for 36 weeks.[41]Co-primary endpoints were percentage change in EASI score from baseline and proportion of patients with EASI-75 at week 36. Patients on dupilumab weekly or q2w showed continued response over time, with insignificant change in percent EASI improvement from SOLO baseline vs. placebo (Table 1). In addition, percent change with the other regimens dose dependently worsened. A significantly higher proportion of patients on dupilumab weekly or q2w maintained EASI-75 vs. patients on placebo (71.6% vs. 30.4%). Longer dosage intervals of dupilumab resulted in diminution of EASI-75 response (58.3% on q4w, 54.9% on q8w). Consistent with the continuous co-primary EASI end point, there was no overall loss of efficacy with dupilumab weekly or q2w (baseline vs. week 35) in percentage change in peak pruritus numeric rating scale (NRS), whereas there was a dose-dependent return of pruritus for the q4w,q8w and placebo groups, particularly after week 12. No new safety signals were identified. These findings confirm dupilumab's efficacy and safety and support the regimen of 300 mg SC q2w for long-term treatment.

In a phase 3 trial in adolescents ages 12-18 years (AD-1526), patients with moderate-to-severe AD were randomized to dupilumab 300 mg SC q4w, 200/300 mg SC q2w (based on weight <60 kg or ≥60 kg, respectively), or placebo.[39]Primary outcomes were percentage of

patients reaching IGA score of 0/1 and percentage of patients achieving EASI-75 at week 16. A greater percentage of adolescents in the treatment arms achieved primary outcomes vs. placebo (Table 1, Figure 3A, 3B). Safety profiles in adolescents were similar to adults, with conjunctivitis and injection site reactions the most common AEs. Furthermore, pooled analysis from laboratory findings from three randomized controlled trials (SOLO-1, SOLO-2, and LIBERTY AD CHRONOS) assessing the need for routine safety testing of dupilumab concluded patients using dupilumab for moderate- to-severe AD do not need routine laboratory testing, as there was no clinically major change in routine laboratory parameters attributed to dupilumab.[42]

Moreover, the effectiveness and safety of dupilumab treatment in real-life clinical setting are comparable to that of clinical trials. Twenty-two unique studies encompassing 3,303 AD patients showed that after 16 weeks of dupilumab therapy, the pooled proportion of patients achieving EASI-75 was 59.8%. Conjunctivitis was the most common adverse event, reported in a pooled proportion of 26.1% compared to 8% in pooled data from clinical trials.[43] This AE seems to be specific to AD, as it was not observed in patients involved in trials assessing dupilumab in conjunction with asthma and nasal polyposis.[44] While it is currently not possible to predict who will develop conjunctivitis during treatment with dupilumab, patients with a history of allergic conjunctivitis seem to have a higher risk. However, the pathophysiology of dupilumab-induced eye disorders remains unknown.[43] Furthermore, biomarker analysis of a cohort study of daily practice dupilumab treatment up to 16 weeks found that treatment with dupilumab also significantly suppressed disease severity-related serum biomarkers thymus-and activation-regulated chemokine (TARC), pulmonary and activation-regulated chemokine (PARC), periostin, and IL-22, and eosinophil related markers eotaxin-1 and eotaxin-3.[45]

In adult patients with moderate-to-severe AD, dupilumab improved their health outcomes compared to best supportive care, and additional costs led to an incremental cost-effectiveness ratio ranging from 28,500 £ (low certainty) to $124,541 (US dollars; moderate certainty), which are still likely to result in overall cost-effectiveness. However, all economic analyses were performed in high-income countries in line with their health system perspectives. Thus, their results may not be applicable to other countries.[46]

Phase 1 and 2 mechanistic studies involving skin biopsies and blood from patients treated with dupilumab vs. placebo showed highly significant changes in the molecular signatures only in patients treated with dupilumab. These included as expected Th2-related products, but also extended to markers related to other immune axes, such as Th17/Th22, but not Th1.[47, 48]A recent meta-analysis approach showed that the molecular improvements with dupilumab in certain immune pathways (such as Th2), are on par to those induced by broad systemic treatments, such as cyclosporine A.[49, 50] Furthermore, a systematic literature review comparing efficacies of systemic therapies for the treatment of AD showed the strongest evidence currently exists for dupilumab and cyclosporine at improving clinical disease severity and quality of life.[51]

Several phase 3 clinical trials indicate that dupilumab is effective in AD, with the response maintained for at least 1 year of continuous treatment in the majority of patients and with a

tolerable safety profile, but showed a higher incidence of conjunctivitis. About one-third of all treated adult patients are clear in IGA from their AD. Up to 70% of patients achieve an EASI-75, and it takes about 4 weeks to reach the full clinical outcome.

Lebrikizumab

Lebrikizumab is a humanized IgG4κ mAb that inhibits IL-13 signaling by binding free IL-13 with very high affinity, blocking ability of IL-13 to bind IL-4Rα. This prevents heterodimerization of IL-4Rα and IL-13 receptor alpha 1 chain (IL-13Rα1) subunits.[52] IL-13 also downregulates filaggrin expression, an integral protein in formation and maintenance of the epidermal barrier.[53]

A phase 2 study assessed the safety and efficacy of lebrikizumab administered subcutaneously at three different doses in adults with moderate-to-severe AD inadequately controlled with TCS and regular emollients for ≥1 month (125 mg single dose, 250 mg single dose, 125 mg q4w, or placebo q4w for 12 weeks after a 2 week period of TCS run-in). At the primary endpoint at week 12, EASI-50 was achieved in patients on 125 mg q4w (82.4%; p=0.026), while a 62.3% response was observed in placebo group treated with TCS. Furthermore, 125 mg q4w treatment showed significantly more patients achieving EASI-75 (54.9% vs. 34.0% placebo; p=0.036) and SCORAD improvements of ≥50% (SCORAD-50) (51.0% vs. 26.4% placebo; p=0.012), while no statistically significant response was seen in the single dose groups. None of the three different doses of lebrikizumab achieved statistically significant improvement in pruritus visual analogue scale (VAS), Atopic Dermatitis Impact Questionnaire, or DLQI. Lebrikizumab was well-tolerated, with only mild-to-moderate AEs. No significant differences in AEs among treatment and placebo groups were seen (66.7%; placebo 66.0%). The most frequent treatment associated AEs included conjunctivitis (9.6%; placebo 8.0%) and herpetic infections (7.7%; placebo 0%).[54]

A 16-week phase 2b study investigated the safety and efficacy of lebrikizumab monotherapy 125 mg SC q4w, 250 mg SC q4w, or 250 SC mg q2w (following a loading dose) for the treatment of moderate-to-severe AD patients with chronic AD ≥1 year and uncontrolled by topical treatments. Patients requiring rescue therapy could use TCS for as brief a period as possible. The study showed significant dose-dependent improvement in average percentage of change in EASI scores and pruritus NRS vs. placebo. Improvements in EASI score were achieved in 62.3% of patients in the 125 mg q4w group (p=0.165), 69.2% of patients in the 250 mg q4w group (p=0.0022), and 72.1% in the 250 mg q2w group (p=0.0005), vs. 41.1% in placebo group. Furthermore, the 250 mg groups showed significant difference vs. placebo in secondary endpoints, including percent with score of 0/1 on IGA, EASI-50, EASI-75, and EASI-90. In addition, no dose-response relationship in treatment emergent adverse events (TEAEs) was observed. Rescue medication was used less in lebrikizumab treated patients vs. placebo (125 mg q4w: 12.3%; 250 mg q4w: 12.5%; 250 mg q2w 13.3%; placebo 34.6%), and lebrikizumab treated patients had shorter duration of topical medication use. AEs were mild-to-moderate, with the most common AEs upper respiratory tract infection (7.5% all lebrikizumab groups, placebo 5.8%) and nasopharyngitis (6.6%; placebo 3.8%).[55]

While phase 2 trials of lebrikizumab demonstrated that blocking IL-13 alone may be sufficient to see the efficacy signals in AD, head-to-head active comparator studies are needed to provide the comparative efficacy of anti-IL-13 therapy alone vs. anti-IL-4/IL-13. Phase 3 trials investigating the long-term safety and efficacy of lebrikizumab as monotherapy of 52 weeks duration for treatment of moderate-to-severe AD is also currently underway. (NCT04146363, NCT04178967, NCT04392154, NCT04250350).

Tralokinumab

Tralokinumab is a fully human IgG4κ mAb binding to unbound IL-13 cytokine with high affinity, similar to lebrikizumab but at a different epitope, preventing IL-13 from binding to both IL-13Rα1 and IL-13Rα2.[56]It was initially developed for the treatment of severe asthma. However, in a phase 2b study, tralokinumab did not significantly reduce asthma exacerbation rates in patients with severe uncontrolled asthma.[57]

In a 12-week phase 2b trial, tralokinumab was studied in moderate-to-severe AD adults. Participants were randomized to receive placebo or tralokinumab SC q2w (45 mg, 150 mg, or 300 mg) with concomitant TCS, after a 2-week run-in period with TCS. At baseline, mean EASI score ranged from 24.8 to 27.3 for all tralokinumab groups and 26.4 for placebo. The 150 mg or 300 mg group achieved clinically significant improvements in EASI scores starting at week 4 vs. placebo. At week 12, the adjusted mean difference from baseline EASI score was significantly different from placebo in patients treated with 150 mg (−4.36; p=0.03) and 300 mg (−4.94; p=0.01). The greatest improvements in IGA score were observed in the 300 mg group but did not achieve statistical significance (26.7% of tralokinumab-treated patients vs. 11.8% placebo; p=0.06). The 300 mg group also had statistically significant difference in secondary endpoints (DLQI, pruritis NRS score, and SCORAD score) vs. placebo.[58]Furthermore, the exploratory analyses stratified the patients by baseline serum biomarkers for IL-13 signaling, including dipeptidyl peptidase-4 (DPP-4) and periostin.[58, 59] Tralokinumab-treated groups in the DPP-4 high and periostin high subgroups had greater improvements in EASI scores vs. the intended to treat (ITT) population. Differences in IGA response for the treatment arm were also improved in the same subgroups vs. ITT population. This presents the concept that the biomarkers DPP-4 and periostin may help identify patients who may have better targeted treatment response. AEs were mild-to-moderate, with the most frequent event upper respiratory tract infection (3.9% all tralokinumab groups; 3.9% placebo). Conjunctivitis was also reported (2.0% 45 mg, 5.9% 150 mg vs. 3.9% placebo). In terms of interpretation of this trial, due to the run-in period and concomitant use of TCS, the real efficacy of this biologic may be confounded[52]. The observed improvements in placebo-treated participants indicate that TCS provided partial benefit, despite all participants having inadequate disease control with such therapy at enrollment. Although a study of tralokinumab monotherapy would provide a more definitive measurement of efficacy than in combination with topical glucocorticoids, in clinical practice it is expected that biologics will be prescribed concomitantly to topical therapies.[52] Phase 3 trials of tralokinumab in adults and adolescents with moderate-to-severe AD have recently been completed with results pending (NCT03131648, NCT03160885, NCT03363854). A phase 3 trial investigating the long-term safety and efficacy of tralokinumab in patients who participated in previous trials is also currently underway

(NCT03587805). Additionally, there is an active phase 3 trial studying the efficacy of tralokinumab used as monotherapy for adolescents with moderate-to-severe AD (NCT03526861).

Nemolizumab

Nemolizumab is a humanized IgG2κ anti-IL31 receptor α (IL31Rα) mAb.[60] IL-31, a proinflammatory cytokine playing an important role in mediating pruritus via overexpression of IL-31 receptors on sensory nerves,[61] is known as a perpetuator of the itch-scratch cycle that results in disruption of the skin barrier in AD.[62] A phase 2b study randomized patients with moderate-to-severe AD and severe AD-associated pruritus uncontrolled by topical treatments to 10 mg, 30 mg, or 90 mg of subcutaneous nemolizumab q4w or placebo until week 20, with a 12-week follow-up period until week 32.[60] Both treatment and placebo groups applied TCS and moisturizers in addition to treatment. At baseline, mean EASI score ranged from 24.2 to 25.9 for all nemolizumab groups and 27.0 for placebo. All groups showed improvement in the primary endpoint, the mean percentage change in baseline EASI at 24 weeks vs. placebo, with the 30 mg group the most effective (−68.8% vs. −52.1%; p=0.016). All doses of nemolizumab also showed statistically significant improvements in peak pruritus NRS as early as week 1 ($p<0.05$), with the most efficacious response seen in the 30 mg treatment arm (67.3% vs. 35.8% placebo at week 24, $p<0.001$). Furthermore, the 30 mg group had significant difference from placebo in secondary endpoints, including percentage of patients achieving EASI-50, EASI-75, and EASI-90 ($p<0.05$). Nemolizumab was well-tolerated and had a good safety profile, with the most common AEs nasopharyngitis, upper respiratory tract infection, and exacerbation of AD. In addition, a dose-dependent increase in asthma related events was observed in patients with a history of asthma. Some of these events might have occurred because effective treatment with nemolizumab led to improved overall well-being and increased activity levels that, in turn, triggered asthma symptoms. All asthma-related events were mild and manageable.

In a 16-week phase 3 trial, Japanese patients with AD and moderate-to-severe pruritus and inadequate response to topical agents and antihistamines were randomized to receive SC nemolizumab (60 mg) or placebo q4w with concomitant topical agents. The primary endpoint was mean percent change in the VAS score for pruritus.[63] At baseline, the median VAS score for pruritus was 75 and median EASI score ranged from 22.7 (placebo) to 24.2 (nemolizumab). At week 16, mean percent change in the VAS score was −42.8% in the nemolizumab group and −21.4% in the placebo ($p<0.001$). However, for the secondary efficacy endpoints, including the change in EASI score and the time course of change in the VAS score for pruritus up to 4 weeks, no adjustments were made for multiple comparisons, from which no clinical inferences can be made. The mean percent change in EASI score was −45.9% with nemolizumab and −33.2% with placebo. At day 15, the percent change in the daily mean VAS score for pruritus was reported as early as day 2 (−10.3% nemolizumab vs. −4.4% placebo). Overall, nemolizumab was well-tolerated, with only mild-to-moderate AEs. Incidence of injection-site reactions was greater with nemolizumab vs. placebo (8% vs. 3%).[63]

A phase 2 study testing the safety and pharmacokinetics of nemolizumab in adolescent patients with AD is ongoing (NCT03921411). Two phase 3 studies are currently recruiting to further test the efficacy and safety profile of nemolizumab in adults with moderate-to-severe AD (NCT03985943, NCT03989349).

Tezepelumab

Tezepelumab is a fully human IgG2λ mAb binding thymic stromal lymphopoietin (TSLP), an epidermal keratinocyte-derived cytokine that activates dendritic cells to induce the production of type 2 cytokines, including IL-4, IL-5, IL-13, and tumor necrosis factor (TNF)-α, and contributes to pruritus in AD by activating cutaneous sensory neurons[64, 65]. Overexpression of TSLP in keratinocytes has been found in patients with acute or chronic AD[66]. High levels of TSLP in the serum have also been observed in children with AD.[67]

In a phase 2a trial, patients were randomized to receive 280 mg tezepelumab SC or placebo q2w with concomitant TCS. However, the study failed to reach statistical significance in the primary endpoint, EASI-50 vs. placebo, at week 12 (64.7% vs. 48.2%; p=0.091).[65] Similarly, only a numerical difference between the two groups in IGA response rate was observed at week 12 (19.3% vs. 12.8%; p=0.36). At other secondary endpoints, including EASI-75, EASI-90, SCORAD, and NRS scores at week 12, patients treated with tezepelumab did not achieve statistically significant improvements vs. placebo. In addition, in an exploratory biomarker subgroup analysis, tezepelumab-treated patients who were DPP-4 high, periostin low, CCL17/TARC low, or IgE high were found to have only numerically greater response at week 12 compared to patients in opposing biomarker subgroups. AEs were comparable between groups and were mild-to-moderate. Most AEs were not considered treatment related, except for injection site erythema. Additional common AEs were nasopharyngitis, diarrhea, upper respiratory tract infection, and headache[65]. Currently, a phase 2b trial is recruiting to assess the safety and efficacy of tezepelumab as monotherapy and adjunct therapy with TCS (NCT03809663).

ISB 830 (previously GBR 830)

ISB 830 is a humanized IgG1 anti-OX40 mAb. Engagement of OX40 with its ligand (OX40L) expressed on antigen presenting cells potentiates effector T cell responses.[10, 68] In a phase 2a trial, the safety and efficacy of ISB 830 was assessed in adults with moderate-to-severe AD and inadequate response to topical treatments. Patients were randomized 3:1 to 10 mg/kg intravenous (IV) ISB 830 or placebo on day 1 (baseline) and day 29. Biopsies were collected on day 1, 29, and 71. Primary endpoints were TEAEs and changes in baseline epidermal hyperplasia and gene expression of lesional biomarkers. Secondary endpoints included percent improvement from baseline in SCORAD, IGA, BSA, and EASI scores. However, the study analyzed statistical differences between treatment groups only in primary endpoints and not in secondary endpoints. ISB 830 was well-tolerated with similar TEAEs between treatment groups (63.0% vs. 63.0%). Nasopharyngitis was the only AEs considered treatment related (8.7%).[43] Biomarker analysis demonstrated that ISB 830 post-treatment lesional skin had significant decline in levels of $OX40^+$ T cells and $OX40L^+$ dendritic cells ($p<0.001$). Furthermore, significant reductions in hyperplasia, epidermal

thickness ($p<0.001$), Keratin 16 (K16) mRNA expression ($p<0.01$), and $Ki67^+$ cells ($p<0.001$) were noted in ISB 830 treated groups by day 71. ISB 830 significantly decreased the mRNA expression of cytokines along the Th1 axis— IFN-γ ($p<0.01$) and CXCL10 ($p<0.001$), Th2 axis—IL-31 ($p<0.05$), CCL11 ($p<0.001$), CCL17 ($p<0.001$), and TSLP receptor (TSPLR) ($p<0.001$), and Th17/Th22 axis—IL-23p19 ($p<0.001$), IL-8 ($p<0.01$), and S100A12 ($p<0.001$). However, other main Th2 (IL-4, IL-13) and Th17/Th22 (IL-17A, IL22) cytokines were not significantly reduced with ISB 830. In terms of secondary outcome measures, the ISB 830 group had a greater proportion of patients achieving EASI-50 vs. placebo (76.9% vs. 37.5%). Similarly, an IGA response was reached by 23.1% of ISB 830 treated groups vs. 12.5% of placebo treated patients at day 71. 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 ISB 830 may provide a novel therapeutic paradigm for patients with moderate-to-severe AD. ISB 830 is currently in phase 2b clinical trial in AD (NCT03568162).

Biologic therapies currently not undergoing trials in AD Fezakinumab

Fezakinumab is a human IgG1λ anti-IL-22 mAb.[69] IL-22, produced by Th22 cells, is involved in epidermal hyperplasia and barrier defects in patients with AD. IL-22 levels have been reported to correlate with AD disease severity and response to AD treatment.[15] A small study of 60 patients with moderate-to-severe AD treated for 10 weeks with fezakinumab SC q2w, with primary endpoint at week 12 and a secondary endpoint at week 20, showed clinical benefit in a portion of patients with severe disease, but not in moderate patients.[69]A follow-up mechanistic study showed that responders were those with high levels of IL-22, whereas patients with low IL-22 levels did not respond, and perhaps even showed an exacerbation.[71] This study suggests the potential for a personalized medicine approach based on distinct molecular mechanisms.

Anti-IL-17 Therapy

MOR106, a mouse and human IgG1 anti-IL-17C mAb, showed promising results from a phase 1 study. Eighty-three percent of AD patients treated with MOR106 achieved EASI-50 vs. less than 20% in the placebo at week 4, with continued improvements in the treatment group over the 10-week follow-up period.[72] However, two phase 2 trials testing the safety, efficacy, and tolerability of MOR106 in patients with moderate-to-severe AD were terminated, as they did not meet primary endpoints (NCT03568071, NCT03864627)[73]. Secukinumab, a human IgG1λ anti-IL-17A mAb, has recently completed phase 2 trial (NCT02594098), with no significant changes in EASI or IGA scores. Another phase 2 trial investigating secukinumab for moderate-to-severe AD recently completed with pending results (NCT03568136).

Omalizumab and Ligelizumab

Omalizumab, a recombinant IgG1κ anti-IgE monoclonal antibody, has been used in AD with variable results. 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 (defined as SCORAD-50, EASI-75, or IGA 0 or reduction by 2 points).[74] Recently, a phase 4 trial in children with severe AD found that omalizumab significantly reduced disease severity and topical steroid use.[75] 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).

Conclusion

Targeted biologic agents play an increasing role in the treatment of AD patients refractory to topical treatments. Compared with the off-label use of immunosuppressant medications, that are still a mainstay of treatment for severe uncontrolled AD in some countries, these novel biologic therapies appear to demonstrate considerably better risk-benefit ratios, although there is little long-term data to date.[76] So far, only dupilumab is FDA approved, for which trials and real-life studies have demonstrated considerable short and mid-term efficacy and safety.[32, 33, 38, 39, 41–44] There is a large unmet need for development of additional monoclonal antibodies targeting distinct immune pathways necessary to increase probability of achieving disease control in AD patients, and combination therapy such as dupilumab plus another systemic immunomodulatory agent and/or phototherapy has not been adequately studied.[77]

Apart from dupilumab, several novel biologic agents have demonstrated promising results in clinical trial. Lebrikizumab, tralokinumab, nemolizumab, and ISB 830 have shown favorable results in achieving improvement in disease severity and multiple endpoint outcomes[26, 54, 55, 58, 60]. Compared to other treatments, nemolizumab appears to be superior in improving pruritus, since it has a rapid onset of pruritus reduction as early as dupilumab, which was within 2 days of treatment initiation[40, 60], and also maintained good long-term effectiveness [78]. Tezepelumab, however, did not show statistically significant changes in primary outcome endpoints.[65]

There are several limitations in analyzing clinical trials in AD. Interpretation of the efficacy of biologics can be confounded by concomitant TCS use, and the clinical application of these drugs are limited, as children were excluded from most AD trials. Therefore, it is imperative that future large-scale studies investigate the efficacy of biologics as monotherapy in children with moderate-to-severe AD. Furthermore, long-term follow-up studies assessing safety and persistence of efficacy of each biologic agent is critical for patients with chronic AD. To further guide treatment decisions and guidelines, network meta-analysis is also necessary to provide the best comparative effectiveness of biologic therapies.

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Abbreviation:

AD	Atopic dermatitis
ACD	Allergic contact dermatitis
AEs	Adverse events
BSA	Body surface area
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI-50	Greater than 50% improvement in EASI score
EASI-75	Greater than 75% improvement in EASI score
EASI-90	Greater than 90% improvement in EASI score
IGA	Investigator’s global assessment
ITT	Intended to treat
mAb	Monoclonal antibody
NRS	Numeric rating scale
SCORAD	Scoring of Atopic Dermatitis
SCORAD-50	Scoring of Atopic Dermatitis improvements of ≥ 50%
SC	Subcutaneously
TCS	Topical corticosteroid
TEAE	Treatment-emergent Intended to treat

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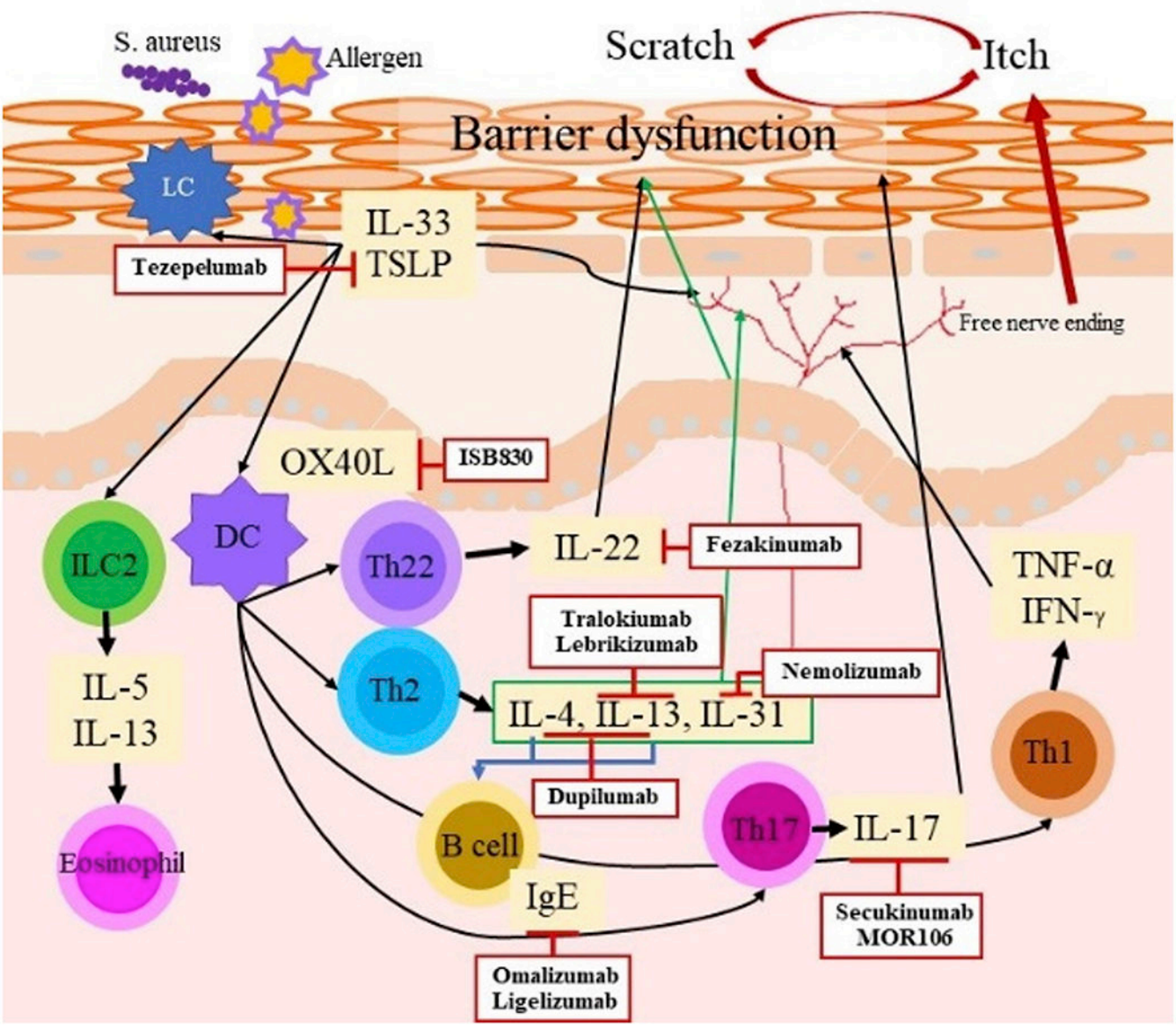

FIGURE 1.

Atopic dermatitis pathogenesis and targets of biologics approved and in clinical development for atopic dermatitis. *DC*, Dendritic cell; *IFN*, interferon; *IgE*, immunoglobulin E; *IL*, interleukin; *ILC*, innate lymphoid cell; *LC*, langerhans cell; *Th*, T-helper; *TNF*, tumour necrosis factor; *TSLP*, thymic stromal lymphopoietin.

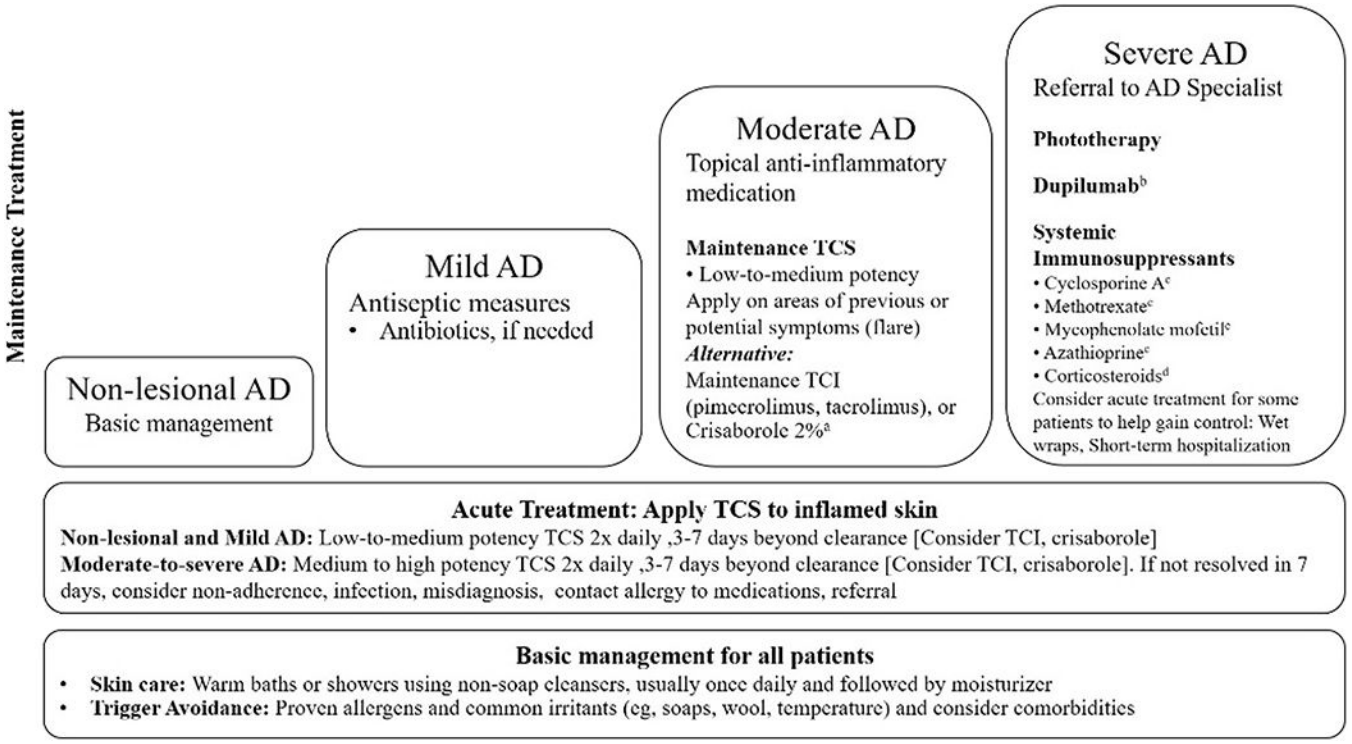

FIGURE 2.

Step-care management of atopic dermatitis (AD). Acute and maintenance treatments for AD across the spectrum of disease severity. [a]For patients aged ≥2 years with mild-to-moderate AD. [b]For patients aged ≥6 years with moderate-to-severe AD. [c]Not approved by the Food and Drug Administration to treat AD. [d]Not recommended for long-term maintenance. *TCI*, Topical calcineurin inhibitor; *TCS*, topical corticosteroid. Adapted from Fishbein et al.[81]

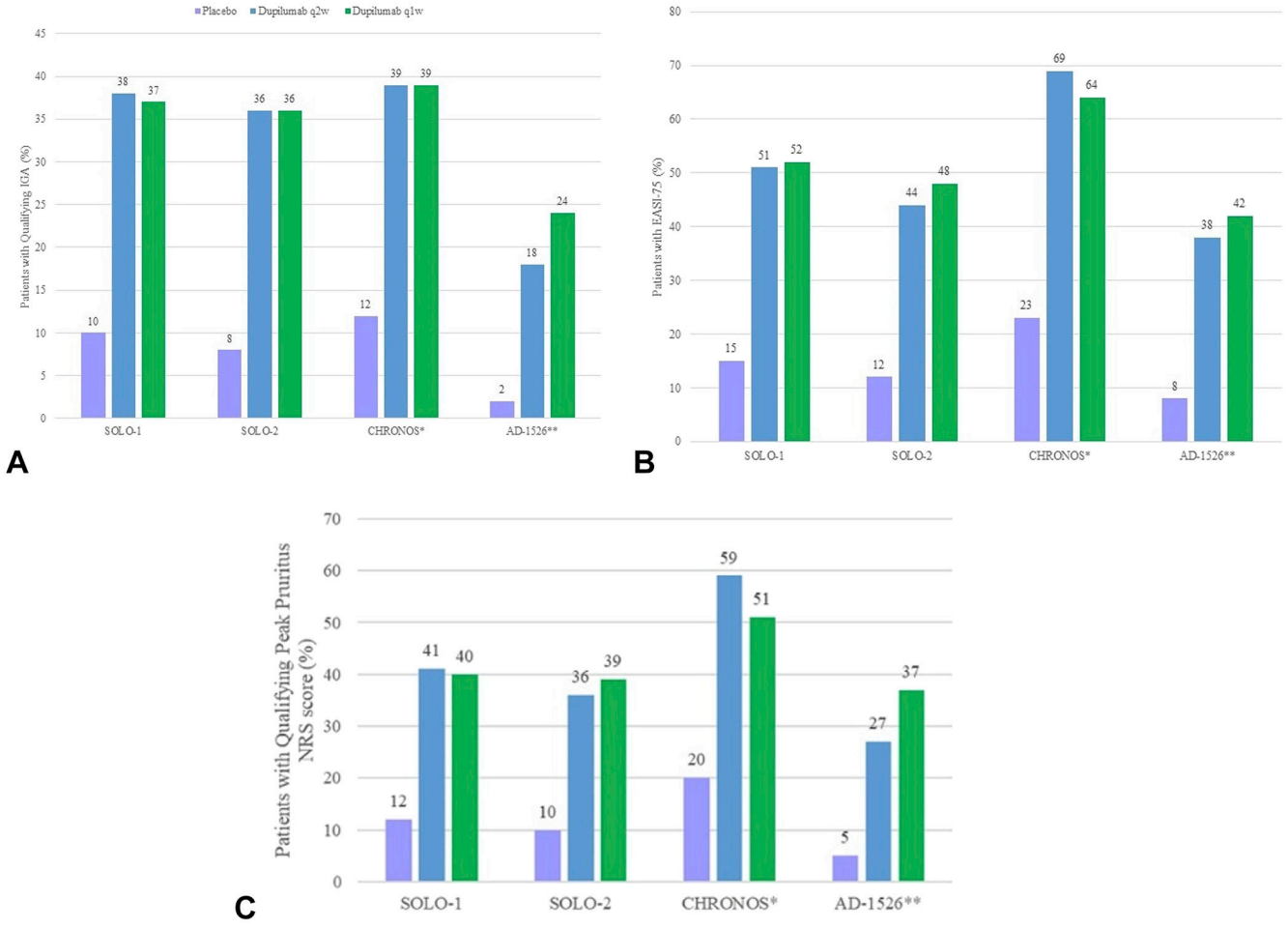

FIGURE 3.

Primary endpoint (**A**) and key efficacy endpoints (**B, C**) of phase 3 trials of dupilumab for the treatment of moderate-to-severe atopic dermatitis. **A**, The proportions of patients who achieved IGA 0/1 with ≥2 reductions from baseline at week 16 among patients who received dupilumab q1w, q2w, or placebo in SOLO 1 and SOLO 2. Proportions of patients who achieved IGA 0/1 at week 16 among were a primary endpoint for AD-1526. **B**, The proportions of patients who achieved EASI-75 at week 16 among patients who received dupilumab and placebo. EASI-75 was a co-primary endpoint in CHRONOS. **C**, The proportions of patients with ≥4-point improvement in peak pruritus NRS score from baseline at week 16 among patients who received dupilumab and placebo. $P < .001$ for all comparisons with placebo in SOLO1/SOLO2. $P < .0001$ for all comparisons with placebo in CHRONOS. $P < .001$ for all comparisons with placebo in AD-1526. *EASI-75*, Greater than 75% improvement in Eczema Area and Severity Index score; *IGA*, Investigator's global assessment; *NRS*, numeric rating scale; *q1w*, every week; *q2w*, every other week. *In CHRONOS, patients also received concomitant topical corticosteroid in every treatment arm. **In AD-1526, patients received dupilumab every 2 weeks (green), every 4 weeks (blue), or placebo.

TABLE 1.

Biologics currently approved or in clinical trials for atopic dermatitis

Drug	Mechanism	Phase trial	N	Age group (y)	Duration (wk)	Concomitant TCS/rescue therapy	Primary endpoint	Adverse events	Current phase of clinical trials underway	Strength of recommendation, grades of evidence*[79,80]
Dupilumab	Anti-IL-4Rα mAb	Phase 3 (SOLO-CONTINUE)	422	≥18	36	No	*Percent change in EASI score (difference between SOLO-CONTINUE baseline and week 36)* Treatment group weekly or q2w: no significant change from SOLO-CONTINUE baseline (−0.06%) q4w: −3.8% q8w: −6.8% Placebo: −21.7% *EASI-75* Weekly or q2w: 71.6%† q4w: 58.3%‡ q8w: 54.9%‡ Placebo: 30.4%	Conjunctivitis (5.4% weekly or q2w, 4.6% q4w 3.6% q8w vs 4.9% placebo), injection-site reactions (10.8% weekly or q2w, 6.9% q4w 7.1% q8w vs 8.5% placebo)	Phase 2: NCT03861455 NCT03346434 Phase 3: NCT02612454 NCT01949311 Phase 4: NCT03667014 NCT03389893 NCT03293030 NCT04447417 NCT04033367	A, 1a[46]
		Phase 3 (AD-1526)	251	12-18	16	Yes	*Percentage of participants achieving an IGA response* 200/300 mg q2w: 24.4%† 300 mg q4w: 17.9%† vs. Placebo: 2.4% *EASI-75* 200/300 mg q2w: 41.5%† 300 mg q4w: 38.1%† vs. Placebo: 8.2%	Conjunctivitis (9.8% q2w, 10.8% q4w vs 4.7% placebo), injection-site reactions (8.5% q2w, 6.0% q4w vs 3.5% placebo)		
Lebrikizumab	Anti-IL-13 mAb	Phase 2b	280	≥18	16	Yes	*Percent change in EASI score* 125 mg q4w: −62.3% 250 mg q4w: −69.2%† 250 mg q2w: −72.1%† vs placebo: −41.1%	Upper respiratory tract infection (7.5% all lebrikizumab groups, placebo 5.8%), nasopharyngitis (6.6% all lebrikizumab groups, placebo 3.8%)	Phase 3 NCT04146363 NCT04178967 NCT04392154 NCT04250350 NCT04250337	B, 2b
Tralokinumab	Anti-IL-13 mAb	Phase 2b	204	18-75	12	Yes	*Change from baseline in EASI score* 150 mg: −4.36‡ 300 mg: −4.94‡	Upper respiratory tract infection (3.9% all tralokinumab groups vs 3.9% placebo)	Phase 3 NCT03587805 NCT03761537 NCT03526861	B, 2b
Nemolizumab	Anti-IL-31Rα mAb	Phase 2b	226	≥18	24	Yes	*Percent change in EASI score* At week 24: Greatest difference in 30 mg dose: −68.8%‡ vs placebo: −52.1%	Dose-dependent increase in asthma exacerbations in treatment group (3.6% 10 mg, 12.3% 30 mg, 17.5% 90 mg vs 1.8% placebo)	Phase 2 NCT03921411 NCT04365387 Phase 3 NCT03985943 NCT03989349 NCT03989206	A, 1b

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Drug	Mechanism	Phase trial	N	Age group (y)	Duration (wk)	Concomitant TCS/rescue therapy	Primary endpoint	Adverse events	Current phase of clinical trials underway	Strength of recommendation, grades of evidence [*79,80]
Tezepelumab	Anti-TSLP mAb	Phase 2a	113	18-75	12	Yes	*EASI-50* Failed to reach statistical significance 280 mg: 64.7% vs placebo: 48.2%	Injection-site erythema (5.4% vs 0% placebo)	Phase 2b NCT03809663	B, 2b
ISB 830	Anti-OX40 mAb	Phase 2a	64	≥18	12	No	*Incidence of TEAEs* Similar across treatment groups ISB 830: 63.0% (29/46) vs Placebo: 63.0% (10/16) *Changes from baseline in biomarkers (epidermal hyperplasia and cytokine) at day 71* Signification reductions in: - hyperplasia measures [†] - mRNA signature for Th1, Th2, and Th17/Th22 axes [†] - $OX40^+$ T cells and $OX40L^+$ dendritic cells [†]	Headache (16%), atopic dermatitis (13%) nasopharyngitis (10%)	Phase 2b NCT03568162	B, 2b

EASI, Eczema Area and Severity Index; *EASI-50*, greater than 50% improvement in EASI score; *EASI-75*, greater than 75% improvement in EASI score; *IGA*, Investigator's Global Assessment; *mAb*, monoclonal antibody; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *q8w*, every 8 weeks; *TCS*, topical corticosteroid; *TEAE*, treatment-emergent adverse event.

[*](Strength of recommendation, Grades of evidence) = (A, 1a/1b), (B, 2a/2b/3a/3b), (C, 4) (D, Expert opinion).[79]

[†]Statistical significance of at least $P < .001$.

[‡]Statistical significance of at least $P < .05$.