



Current and Future Monoclonal Antibodies in the Treatment of Atopic Dermatitis

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Abstract

Atopic dermatitis is a common immunologic skin disease. Mild atopic dermatitis can be managed with emollients and topical therapies such as low potency topical steroids, which have a favorable safety profile. Severe atopic dermatitis, in contrast, is a challenging disease to treat. Topical therapies are typically inadequate for control of severe atopic dermatitis. When topical therapies fail, the mainstay of therapy for severe atopic dermatitis has traditionally been phototherapy or off-label use of systemic immunosuppressant treatment, yet systemic immunosuppressants all have significant potential toxicities, drug interactions, and contraindications, requiring close monitoring. Targeted biologics are therefore attractive treatment options for topical therapy-refractory cases of atopic dermatitis, with the potential to offer effective, safer treatment of uncontrolled atopic dermatitis. Dupilumab, as the only biologic therapy currently FDA-approved for atopic dermatitis, is effective for many patients, but there is need for continuing study of additional biologic therapies to address the needs of diverse patients with uncontrolled atopic dermatitis.

Keywords Atopic dermatitis · Eczema · IgE · IL-5 · IL-4 · IL-13 · Thymic stromal lymphopoietin (TSLP)

Abbreviations

AD	Atopic dermatitis
ADIQ	Atopic dermatitis impact questionnaire
EASI	Eczema area and severity index
IGA	Investigator global assessment
PGA	Physician's global assessment
SCORAD	SCORing Atopic Dermatitis
SQ	Subcutaneously
VAS	Visual analog scale

Introduction

Atopic dermatitis (AD) is a very common immune-mediated skin disease, occurring in 10–20% of children, and in 3–6% of adults in the USA [1–4]. It is characterized by eczematous

lesions, xerosis, and pruritus. Mild atopic dermatitis often may be controlled satisfactorily with emollients and low potency topical steroids which have a relatively benign side effect profile. However, many cases severe atopic dermatitis have required treatment with systemic anti-inflammatory drugs such as oral corticosteroids and cyclosporine, which have broad immunosuppressive activities and significant side effects. Phototherapy is another treatment option for moderate-to-severe atopic dermatitis, but its use is limited in some cases by cost, local availability, and patient adherence to therapy [5].

Targeted biologics are therefore attractive treatment options for topical therapy-refractory cases of atopic dermatitis. These include anti-cytokine therapies targeting the inflammation that substantially contributes to the pathogenesis of treatment-refractory atopic dermatitis. Atopic dermatitis involves predominately Th2-mediated inflammation, but varying degrees of involvement of Th1- and Th17-mediated disease is also present. Biologics that have target individual components of these inflammatory pathways have been demonstrating various degrees of success in treating atopic dermatitis (Table 1).

Increased levels of Th2 cytokines including IL-4, IL-5, and IL-13 have been identified locally in active atopic dermatitis lesions [6, 7]. Polymorphisms in the genes encoding IL-4 and

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Table 1 Biologics currently approved or in development for atopic dermatitis

Drug name	Target	Outcome of most recent clinical trials in AD	Current phase of active clinical trials underway
Dupilumab	IL-4R α	Two phase 3 studies in adults—300 mg dupilumab qweekly or q2wks (with loading dose) as monotherapy showed significant improvement versus placebo in the primary endpoint (proportion of patients who had both a score of 0 or 1 on IGA and a reduction of 2 + points in IGA from baseline at week 16). Both groups also had statistically significant improvement compared with placebo in secondary endpoints (EASI75, EASI50, EASI90, body-surface area affected, pruritis score, Dermatology Life Quality Index, Patient-Oriented Eczema Measure and SCORAD) (46).	FDA-approved (ages 6 + years)
Benralizumab	IL-5R α	Not applicable	Phase 2
Lebrikizumab	IL-13	Phase 2b study in adults—125 mg q4wks, 250 mg q4wks, or 250 mg q2wks lebrikizumab (all with loading dose) showed dose-dependent, statistically significant improvement versus placebo in primary endpoint (EASI). The 250 mg groups had significant difference from placebo in secondary endpoints (percent with score of 0 or 1 on IGA, EASI50, EASI75, EASI90), and the 250 mg q2wk group had significant difference from placebo in pruritis score improvement of ≥ 4 points from baseline and change in body-surface area affected from baseline (59).	Phase 3
Tralokinumab	IL-13	Phase 2b study in adults—150 mg or 300 mg tralokinumab q2wks combined with topical steroid showed significant improvement versus placebo in one primary endpoint (EASI) but did not achieve statistical significance in the second primary endpoint (change in IGA). The 300 mg group also had statistically significant difference in secondary endpoints (Dermatology Life Quality Index, pruritis score, SCORAD). Subgroup with high biomarkers for IL-13 showed greater improvements compared with placebo in intention-to-treat analysis (53).	Phase 3 recently completed
Tezepelumab	TSLP	Phase 2a study in adults—280 mg q2wks tezepelumab combined with topical steroid failed to reach primary endpoint (EASI50 responders) versus placebo (67).	Phase 2b
Nemolizumab	IL-31R α	Phase 2b study in adults—10 mg, 30 mg or 90 mg q4wks nemolizumab (with loading dose) combined with topical steroid showed statistically significant improvement versus placebo in primary endpoint (EASI), with maximum difference in the 30 mg group. The 30 mg group had significant difference from placebo in secondary endpoints (percent with score of 0 or 1 on IGA, EASI50, EASI75, EASI90, SCORAD, pruritis score improvement of ≥ 4 points from baseline, Dermatology Life Quality Index, change in weekly average sleep disturbance) (76).	Phase 3 Phase 2 (adolescents)
ISB 830 (GBR 830)	OX40	Phase 2a study in adults—10 mg/kg GBR 830 on day 1 and 29 showed similar rates of adverse events to placebo, except for 8.9% of GBR 830 patients with postprocedural infection versus 0% of placebo. GBR 830 showed significant reductions from baseline in epidermal thickness, decreased markers of epidermal proliferation versus placebo, and differentially decreased mRNA expression from baseline of several Th1 (IFN- γ), Th2 (CCL11, CCL17), and Th17 (IL23p19, S100) cytokines and chemokines compared with placebo (69).	Phase 2b
Risankizumab	IL-23	Not applicable	Phase 2

IL-13 have also been associated with atopic dermatitis [8, 9]. IL-31 is a Th2 cytokine which contributes to pruritus, and is found at high levels in new acute atopic dermatitis lesions [10].

Th22-mediated inflammation is now recognized to be an important component of atopic dermatitis pathology. IL-22 disrupts normal keratinocyte differentiation and promotes epithelial hyperplasia, by downregulating filaggrin and loricrin genes, and instead increasing expression of S100A7, S100A8, and S100A9 [10]. IL-22 levels have been shown to correlate with disease severity, as well as to the level of clinical control achieved with therapy [11, 12].

Chronic atopic dermatitis frequently results in additional inflammation via a Th1 immune response, along with continued presence of Th2- and Th22-mediated inflammation [10].

The cytokine profile of chronic AD features the production of TNF- α level and upregulation of proinflammatory cytokine levels, such as IL-1, IL-6, and IL-8. IL-16 has been shown to play a role in the exacerbation of chronic adult AD, as its levels are significantly higher in adult patients with AD compared with control groups [13].

Current Non-biologic Therapies for Uncontrolled AD

Patients who do not achieve clinical improvement with optimal basic skin care management trigger avoidance, and topical therapies may require treatment with phototherapy or systemic immunosuppressant treatment. These therapies, widely

available for transplant and rheumatological indications, are all currently used off-label for adults with atopic dermatitis and have been studied to varying degrees in pediatric patients as well. Systemic therapies including cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil all have significant potential toxicities, drug interactions, and contraindications. They are therefore recommended to be prescribed by physicians experienced in the management of systemic immunosuppression. The American Academy of Dermatology guidelines outline the essential baseline monitoring and continued weekly then monthly monitoring that are recommended when using these therapies [14].

Phototherapy

Phototherapy is a well-established second line therapy for atopic dermatitis when emollients, topical steroids, and topical immunomodulators fail. It is a recommended treatment modality for both adults and children. Its use in atopic dermatitis was first described in 1978 when Morison et al. reported success in treating patients with oral psoralen and UV light [15]. Since then, multiple studies of UV phototherapy established its efficacy for treatment of AD. However, standardized therapeutic guidelines for UV phototherapy were lacking, leading Meduri et al. [16] to systematically review the medical literature to provide recommendations for use of UV phototherapy. Of the available modalities reviewed, UVA1 was found to be the most efficacious modality with maximal clinical response usually within 2 weeks of treatment. However, therapeutic response usually does not persist beyond 2 to 3 months, and this treatment modality has limited availability. Consequently, the more widely available, narrow-band UVB is more commonly recommended due to its low risk profile, relative efficacy, and broad availability. Adverse effects include actinic damage, local erythema and tenderness, pruritis, and burning and stinging. Non-melanoma skin cancer, melanoma, lentigines, photosensitive eruptions, folliculitis, photoonycholysis, herpes simplex virus reactivation, and facial hypertrichosis are less common possible effects. Despite its effectiveness as a treatment for atopic dermatitis, phototherapy is limited by cost, availability, and side effect profile.

Cyclosporine

Systemic immunomodulatory agents, including cyclosporine, are indicated when topical agents with or without phototherapy have failed or if the patient's skin disease has significant impact on quality of life. Cyclosporine is an immunosuppressant of T cells and interleukin-2 production. It reduces T cell activation through the inhibition of calcineurin, which results in reduced transcription of cytokine genes including interleukin (IL)-2, TNF, and others [17]. It has been found to be an efficacious option showing significant decrease in disease activity within two to 6 weeks of treatment, with one study

showing a mean decrease in total body severity assessment of 55% compared with an increase of 4% in placebo patients [18]. Adverse effects include infection, nephrotoxicity, hypertension, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma. Its use may also be limited in medically complex patients on given the potential for drug interactions.

Azathioprine

Azathioprine is purine-mimic antimetabolite; its net effect is to inhibit DNA, RNA, and protein synthesis which has preferentially deleterious effects on highly proliferating cells such as B cells and T cells. It is used for treatment of refractory atopic dermatitis. In one study after 12 weeks of azathioprine, a treated group reported 37% improvement in moderately to severely affected AD patients compared with placebo [19]. Commonly, however, it can produce intolerable gastrointestinal side effects including nausea and vomiting, bloating, cramping, and anorexia. Other effects include headache, hepatotoxicity, and leukopenia requiring ongoing laboratory monitoring.

Methotrexate

An antifolate metabolite that blocks the synthesis of DNA, RNA and purines, and methotrexate diminishes inflammation likely through several mechanism. It has been compared with azathioprine in a randomized trial that looked at effects at 12 weeks of therapy which showed statistically significant clinical improvement that were comparable between the two groups [20]. This one trial deemed methotrexate to be equally efficacious as azathioprine for severe atopic dermatitis. Other studies have also concluded that methotrexate is efficacious, but inconsistencies between study methods, dosing, and duration of therapy are apparent in the literature. As with other immunomodulators, gastrointestinal side effects are prevalent, limiting patient tolerance of the oral preparation. Additionally, more severe adverse effects such as bone marrow suppression and pulmonary fibrosis are known to occur, and risks of skin cancer and lymphoma have also been reported. The potential for pulmonary fibrosis with short- or long-term use necessitates the need for pulmonary function studies, in addition to liver function tests due to concerns regarding hepatotoxicity.

Mycophenolate Mofetil

Much like azathioprine, mycophenolate inhibits the proliferation of highly proliferative lymphocytes through its action of blocking purine biosynthesis. It inhibits inosine monophosphate dehydrogenase which is an enzyme required for de novo synthesis of guanine nucleotides. Several studies are available that establish mycophenolate as an alternative

therapy for AD. In one such study Murray and Cohen reported a retrospective chart analysis that showed disease improvement in 17 of 20 patients within the first month of treatment, ten of these patients achieved disease clearance [21]. Like azathioprine nausea, vomiting, and abdominal cramps are common side effects. Other possible risks include cytopenia, increased infections, cutaneous malignancy, and lymphoma.

Crisaborole

Crisaborole is a boron-based molecule that enhances cellular control of inflammation by inhibiting PDE4. This prevents the degradation of intracellular cyclic adenosine monophosphate, suppressing the release of cytokines through its effect on downstream regulation of nuclear factor- κ B and nuclear factor of activated T cell signaling pathways. It is a topical based treatment that penetrates human skin well and is substantially metabolized to inactive metabolites thus limiting systemic exposure. Two phase 3, multicenter, randomized, double-blind, vehicle-controlled clinical studies conducted in the USA (AD-301 and AD-302) assessed the safety and efficacy of crisaborole in patients with mild to moderate AD [22]. Patients age greater than or equal to 2 years of age were treated with crisaborole 2% ointment twice daily for 28 days. The primary endpoint was an Investigator's Static Global Assessment (ISGA) score at day 29 of clear (0)/ almost clear (1) with two-grade or greater improvement from baseline. Crisaborole treated patients had a rate of success; AD-301 32.8% vs. 25.4%, ($P = 0.38$); AD-302: 31.4% vs 18% ($p < 0.001$) that was greater than vehicle treated patients. Adverse effects were mild, with the most significant being application site related burning or stinging. These mild local side effects were similarly to those observed with topical corticosteroids and topical calcineurin inhibitors, however with rates being much lower for crisaborole compared with reported rates of TCS or TCI.

Available and Investigational Biologic Therapies for AD (See Table 1)

Anti-IgE Therapies

Serum IgE is elevated in many patients with atopic dermatitis. Omalizumab, as an anti-IgE monoclonal antibody, has been investigated for use in atopic dermatitis. However, its overall efficacy in this condition has been questionable, and omalizumab is not FDA-approved for atopic dermatitis. Initially, in the early 2000s, multiple small case series suggested that omalizumab may have a role in the treatment of atopic dermatitis. Clinical improvement and improved EASI (Eczema Area and Severity Index) or SCORAD (SCORing of Atopic Dermatitis) scores and quality-of-life scores were

described in various case series [23–27]. However, two randomized controlled trials, also both very small in size, did not demonstrate efficacy for omalizumab in atopic dermatitis [28, 29]. Heil et al. demonstrated that omalizumab treatment resulted in decreased IgE+ cells in eczematous skin compared with controls but no significant difference in clinical disease [29]. Iyengar et al. demonstrated decreased serum concentrations of cytokines TARC, TSLP, OX40L, and IL-9 in children with atopic dermatitis treated with omalizumab compared with those treated with placebo. However, the clinical outcomes as measured by SCORAD were similar for omalizumab- and placebo-treated subjects [28]. No further active clinical trials appear to be ongoing to investigate the use of omalizumab in atopic dermatitis.

Other anti-IgE molecules are in development, including ligelizumab (QGE031), which binds IgE with higher affinity than omalizumab. Ligelizumab was studied in patients with moderate to severe atopic dermatitis, in a Phase 2 trial, but results are not available [30].

Tumor Necrosis Factor-Alpha Inhibitors

Th1-mediated inflammation can be a significant contributor to certain forms of atopic dermatitis, especially chronic atopic dermatitis. TNF-inhibitors have been used successfully in psoriasis, inhibiting the Th1- and Th17-mediated inflammation in that skin disease. Multiple TNF-inhibitors are currently on the market and approved for use in psoriasis, including infliximab, adalimumab, etanercept, certolizumab, and golimumab. The few case series examining the use of TNF-inhibitors in atopic dermatitis have yielded disappointing results. Jacobi et al. trialed infliximab in nine patients with treatment-refractory atopic dermatitis. Interestingly, all nine patients experienced initial improvement during the induction phase of therapy, but only two of nine patients had sustained improvement during the maintenance phase [31]. Cassano et al. described long-term control of symptoms with infliximab use in a single adult patient with severe atopic dermatitis [32]. Buka et al. described lack of efficacy of etanercept in two cases of pediatric atopic dermatitis [33], while Rullan et al. reported clinical improvement in chronic atopic dermatitis in another two patients receiving etanercept [34].

Rituximab

Rituximab is an anti-CD20 monoclonal antibody, designed to deplete B cells yet spare preexisting long-lived antibody-producing plasma cells. Several small case series described the use of rituximab in treatment-refractory atopic dermatitis, with few patients experiencing improvement with therapy. Simon et al. described six patients with clinical improvement in eczema score following two intravenous infusions of rituximab 1000 mg, 2 weeks apart [35]. Sediva et al. described two patients who received two doses of rituximab 500 mg, 2 weeks

apart; one patient had improved SCORAD, but the other experienced worsening of their atopic dermatitis [36]. McDonald et al. reported lack of efficacy of rituximab in three adults with severe, treatment-refractory atopic dermatitis [37].

Anti-IL5 Therapies

Eosinophils are well-recognized as a component of the inflammatory infiltrate in both acute and chronic atopic dermatitis. Tissue eosinophils in atopic dermatitis are found in an activated state, releasing granule contents including eosinophil cationic protein and eosinophil derived neurotoxin [38]. Increased levels of these proteins correlate with AD disease activity and decreasing levels are associated with clinical improvement in AD [39–41]. Based on these findings, biologic therapies targeting eosinophilic inflammation, namely anti-IL-5 therapies, were considered potential treatments for atopic dermatitis. Several biologic therapies targeting IL-5 are currently on the market including mepolizumab, reslizumab, and benralizumab. Of these, only mepolizumab has been studied in clinical trials for atopic dermatitis and has not been found to have significant benefit in this disease state.

A randomized, double-blind, placebo-controlled, parallel group study of mepolizumab from January until July of 2002 enrolled forty-three patients between the ages of 18–57 with atopic dermatitis [42]. Patients were given either IV 750 mg mepolizumab or placebo for 2 doses separated by 7 days. The study duration was for 30 days with clinical monitoring of symptoms and laboratory assessment. Patients were not allowed to use other treatments for atopic dermatitis except for nonmedicated emollient and bath oil. There were 20 patients assigned to the mepolizumab group and 23 to placebo. Three patients (2 from mepolizumab group and 1 from placebo) withdrew before 14 days due to AD exacerbation or lack of therapeutic response. While there was a significant decrease in the blood eosinophil level in mepolizumab group, this did not correlate with improvement in clinical endpoints identified in this study. Four out of 18 patients (22.2%) in the mepolizumab group versus 1 of 22 (4.8%) in the placebo group achieved “marked improvement” in AD activity by physician’s global assessment (PGA) score by day 14. This finding was not statistically significant. Overall, 72% of mepolizumab group had either “modest” or “marked” improvement on PGA compared with 41% of placebo ($p < 0.05$). There was larger decrease in SCORAD at day 14 in the mepolizumab group vs placebo but this was not significant. There was no difference in pruritus scores between the two groups. The side effect of mepolizumab group was mild and temporary and not different when compared with placebo.

The most recent phase 2 trial of mepolizumab, recruiting moderate to severe atopic dermatitis subjects between the ages of 18–70, was terminated early in December 2017 [43]. Despite this lack of success in the use of mepolizumab to date

in treatment of atopic dermatitis, phase 2 clinical trials for benralizumab in atopic dermatitis are being pursued.

Dupilumab

A key feature of atopic dermatitis is upregulation of IL-13 and IL-4 in lesional and nonlesional skin [44, 45], and polymorphisms in the genes encoding IL-4 and IL-13 have also been associated with atopic dermatitis [8, 9] (Fig. 1). These findings suggested that both cytokines may contribute to the pathogenesis of atopic dermatitis, and prompted study of an inhibitor of these major Th2 cytokines.

Dupilumab is a monoclonal antibody against IL-4R α , which is a component of both the IL-4 receptor and the IL-13 receptor. Dupilumab was approved for use in atopic dermatitis in March of 2017, as the first monoclonal antibody licensed for use in AD. Dupilumab has been found to be highly effective for the treatment of moderate-to-severe atopic dermatitis. Phase 3 trials consisted of two randomized, double-blind, placebo-controlled, parallel-group trials of identical design in adults with moderate-to-severe atopic dermatitis in North America, Europe, and Asia (SOLO 1 and SOLO 2). Dupilumab was used as monotherapy in these trials, and subjects discontinued use of any topical steroids, calcineurin inhibitors, immunomodulating biologic agents, systemic steroids, and nonsteroidal systemic immunosuppressants. The studies examined two dupilumab arms vs placebo; a loading dose of 600 mg subcutaneously followed by 300 mg SQ weekly for 16 weeks, or a loading dose of 600 mg SQ followed by 300 mg SQ every other week for 16 weeks [46]. In both studies, dupilumab achieved its primary endpoint of significantly more patients than placebo with an Investigator’s Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and an improvement of 2 points or more on the IGA from the baseline score at week 16. In SOLO 1, the primary endpoint was achieved in 38% receiving dupilumab every other week and 37% receiving weekly dupilumab, versus 10% receiving placebo. In SOLO 2, the primary endpoint was reached in 36% receiving dupilumab either every week or every other week, compared with 8% receiving placebo. Multiple secondary endpoints were also reached, including EASI50, EASI75, EASI90, SCORAD, change in body-surface area affected, and decrease in pruritus numerical rating scale. Several quality-of-life and depression scales that were used in these studies also showed statistically significant differences from placebo.

The safety profile of dupilumab in these trials appears good. Serious adverse events did not occur at a higher rate than for placebo, and most other adverse events also occurred at a similar rate to placebo. Conjunctivitis (either allergic or unspecified cause) was reported at a higher rate in participants receiving dupilumab compared with placebo, as were injection site reactions. The incidence of conjunctivitis in patients treated with dupilumab was reported to be as high as 14% in

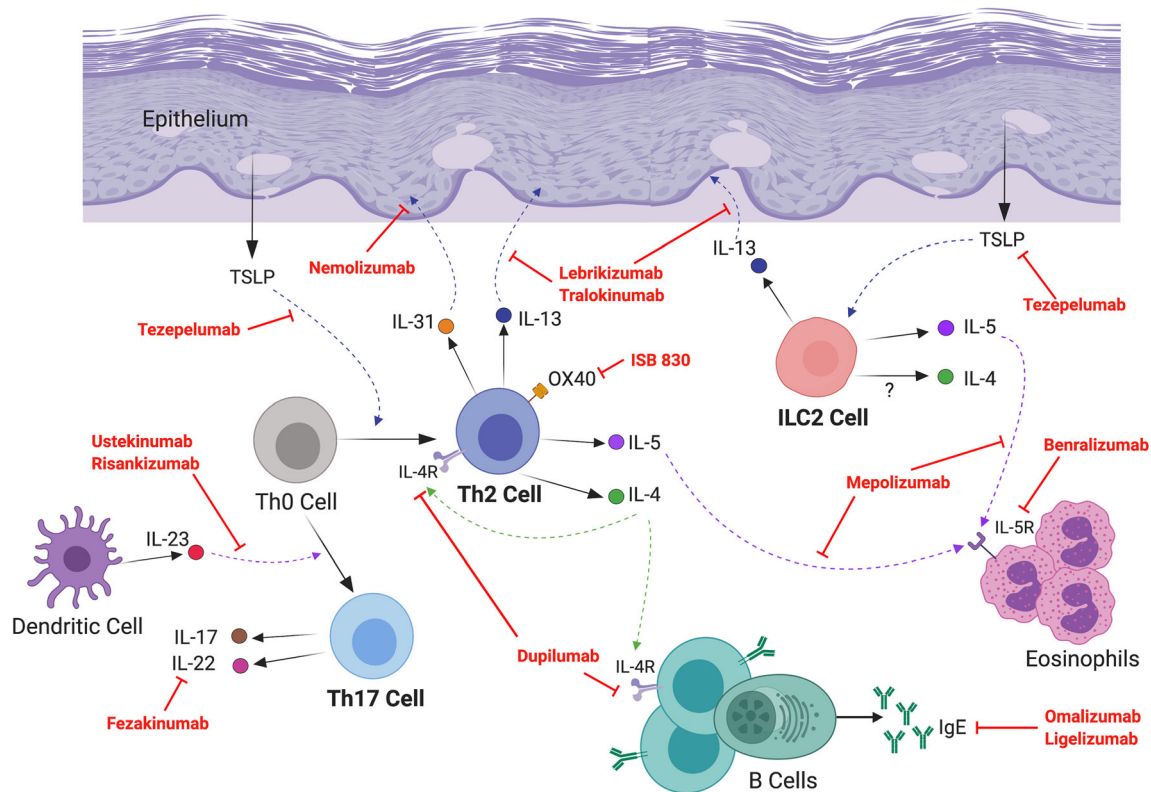


Fig. 1 Targets for biologic therapies available or under investigation for use in atopic dermatitis

LIBERTY AD CRONOS the 1 year, randomized, double-blinded, placebo-controlled phase 3 trial. This adverse effect was further characterized in a case series of 12 patients who reported development of conjunctivitis from a cohort of 142 patients treated with dupilumab, with a reported mean time of 15.8 weeks from treatment initiation to development of conjunctivitis symptoms [47]. Three of these patients developed severe conjunctivitis with one needing to stop the drug permanently. All patients showed improvement in their AD at the time of conjunctivitis diagnosis, with 75% of patients having severe baseline AD with an IGA score of 4. Interestingly, this complication is not observed when dupilumab is used for asthma [48].

Another phase 3 study has evaluated dupilumab in combination with topical steroids in adults with moderate to severe AD [49]. Again, dupilumab was compared with placebo at either a loading dose of 600 mg subcutaneously followed by 300 mg SQ weekly, or a loading dose of 600 mg SQ followed by 300 mg SQ every other week. The trial lasted for 52 weeks, and primary endpoint of Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and an improvement of 2 points or more on the IGA from the baseline was achieved for both treatment arms. Multiple secondary endpoints were also achieved, and adverse event profile was very similar to that seen in SOLO 1 and SOLO 2. Injection site reactions and conjunctivitis were the two adverse events seen at a significantly higher rate in dupilumab versus placebo.

Based on these trials, dupilumab has been approved by the FDA for use in adolescents and adults with moderate-to-severe AD, as an every-other-week subcutaneous injection with initial dose of 600 mg followed by 300 mg every other week. Stage 3 trials have also shown dupilumab to be effective in pediatric patients ages 6 to 11 years with moderate or severe atopic dermatitis, and the product has now been approved for treatment of AD in this age group [50].

In adult patients with moderate-to-severe atopic dermatitis, dupilumab may also be cost-effective. A cost-utility analysis was conducted that showed that dupilumab improved health outcomes compared with usual care, and additional costs lead to an incremental cost-effectiveness ratio (ICER) below commonly cited thresholds for cost-effectiveness [51]. In this study, a lifetime Markov model from a US payer perspective was developed that categorized patient's health states based on treatment response. These groups represented treatment response defined by percentage decrease in EASI score after a patient began treatment with either dupilumab or usual care with emollients. Treatment effectiveness was modeled by the probability of entering EASI50, EASI75, and EASI90 states after treatment was started. Using the manufacturer estimated net price of \$224,300 for dupilumab drug costs and \$241,800 in other healthcare costs, the total lifetime costs per patient was estimated to be \$466,200 for treatment. This led to an ICER of \$101,800/QALY, with dupilumab providing an additional 1.91 QALYs for this population. Lifetime costs of

usual (emollient) care were \$271,500. The ICER for those with severe disease was lower (\$78,300/QALY net price) compared with moderate AD (\$130,800/QALY). Those with moderate AD tended to have high response rates to dupilumab and thus were on the drug for longer, leading to higher costs. For the base case (moderate and severe cases combined), investigators found that dupilumab improves health outcomes with additional costs that are still likely to result in overall cost-effectiveness.

Anti-IL-13 Therapy

With the success of dupilumab in atopic dermatitis, it will be informative to determine the contribution of IL-4 blockade or IL-13 blockade individually, in contrast to blockade of both receptors. Two monoclonal antibodies that exclusively target IL-13, tralokinumab, and lebrikizumab are currently in clinical trials for AD.

Tralokinumab is an IL-13 neutralizing antibody, which blocks the binding of IL-13 to IL-4R α and IL-13R α 1 (the two subunits of the IL-13 receptor), as well as to the IL-13R α 2 decoy receptor [52]. In a 12-week phase 2 placebo-controlled trial, tralokinumab was studied in moderate-to-severe atopic dermatitis at doses of 45 mg, 150 mg, and 300 mg subcutaneously every 2 weeks [53]. The treatment arms receiving 150 or 300 mg of tralokinumab subcutaneously every 2 weeks for 12 weeks achieved clinically significant improvements in EASI scores from week 4 onward. However, there was no significant difference from placebo in the second primary endpoint, percentage of subjects achieving IGA response of 0 (clear) or 1 (almost clear). Significant improvement in several secondary endpoints were seen in the treatment arms, including improvement in SCORAD, SCORAD50 (proportion of patients achieving SCORAD improvements of $\geq 50\%$), EASI50 (proportion of patients achieving EASI improvements of $\geq 50\%$), EASI75 (proportion of patients achieving EASI improvements of $\geq 75\%$), and pruritus numeric rating scale.

The most frequent study drug-related adverse events were upper respiratory tract infection and headache. There was one report of oral herpesvirus that was felt to be drug-related in a treatment arm. Phase 3 trials of tralokinumab in adults and adolescents with atopic dermatitis have just been completed, with results pending [54–56].

Lebrikizumab is an anti-IL-13 monoclonal antibody which binds to IL-13 with very high affinity, blocking IL-13 binding to IL-4R α . This prevents association of IL-4R α and IL-13R α [57]. A phase 2, placebo-controlled trial investigated lebrikizumab at three different doses in adults with moderate to severe atopic dermatitis; 125 mg as a single dose, 250 mg as a single dose, or 125 mg once every 4 weeks for 12 weeks [58]. The 125 mg every 4 weeks treatment arm demonstrated significantly more patients achieving both EASI50 and

EASI75 versus placebo, while the response to single doses of lebrikizumab was not statistically significant. The lebrikizumab 125 mg single dose and 125 mg q4week arms also showed statistically significant improvement in sleep loss visual analog scale (VAS), but none of the three lebrikizumab arms achieved statistically significant improvement in either pruritus VAS, Atopic Dermatitis Impact Questionnaire (ADIQ), or Dermatology Life Quality Index.

A 16-week phase 2b randomized trial investigated lebrikizumab monotherapy given as 125 mg every 4 weeks, 250 mg every 4 weeks, or 250 mg every 2 weeks (following a loading dose) for the treatment of moderate-to-severe atopic dermatitis. The study demonstrated a significant dose-dependent improvement in average percentage of change in EASI scores and pruritus NRS (numeric rating scale) versus the placebo group [59]. Phase 3 trials of lebrikizumab in moderate-to-severe atopic dermatitis are currently underway [60, 61].

Anti-TSLP Therapy

Thymic stromal lymphopoietin (TSLP) is a cytokine produced by keratinocytes. It drives dendritic cells to promote Th2 polarization, likely acting as a switch to turn on allergic inflammation [62, 63]. TSLP also acts directly on certain cutaneous sensory neurons, contributing to pruritus in AD [64]. There is evidence that TSLP may trigger the onset of AD, in childhood as well as drive the atopic march toward development of further atopic diseases [65, 66]. Tezepelumab is an anti-TSLP antibody that is under evaluation as an atopic dermatitis treatment. A phase 2a trial in adult atopic dermatitis failed to achieve its primary endpoint, superiority over placebo in EASI50 [67], but tezepelumab continues to be explored as a treatment for atopic dermatitis, and is in a phase 2b study investigating its use as a monotherapy for moderate-to-severe AD [68].

Anti-OX40 Therapy

OX40 (CD134) is a costimulatory molecule of the TNF receptor/TNF superfamily, found on effector T cells and regulatory T cells. OX40 ligand (OX40L; CD252) is expressed on activated antigen-presenting cells, and engagement of OX40 with its ligand augments effector T cell responses triggered through the T cell receptor. In the skin of patients with AD, OX40L+ dendritic cells are increased compared with psoriatic and normal skin. Recently, a phase 2a clinical trial of GBR 830, a humanized IgG1 mAb targeting OX40, was published [69]. In this randomized, double-blind, placebo-controlled, repeated-dose trial, patients with moderate-to-severe AD were randomized 3:1 to 10 mg/kg intravenous GBR 830 or placebo. Forty-six patients received the investigational drug on day 1 and 29, and were followed out to day

85. Biopsies were collected on day 1 before treatment and again after treatment on day 29 and/or 71. Primary endpoints included treatment-emergent adverse events, as well as changes from baseline in biomarkers (epidermal hyperplasia/cytokine mRNA expression) on biopsy. Secondary endpoints included percent improvement from baseline in SCORAD, IGA, BSA, and EASI scores.

GBR 830 was found to be well tolerated with similar overall treatment-emergent adverse events compared with placebo. Infection following a procedure occurred in four subjects in the GBR 830 group, one of these infections after tooth extraction, other three were secondary infection at the skin biopsy site. In contrast, no post-procedural infections occurred in the placebo group. Epidermal hyperplasia measures at day 71 were significantly lower in the GBR 830 group compared with placebo, and GBR 830 subjects had significant decrease in epidermal hyperplasia compared with baseline at day 29 and day 71. Compared with placebo, GBR 830 lesional biopsies showed significant decreases in several Th1- (INF- γ), Th2- (CCL11 and CCL17), and Th17-related (IL-23p19 and S100A12) mRNAs. At day 71, the GBR 830 group had a greater proportion of patients achieving 50% or greater improvement in EASI versus placebo (76.9% vs 37.5% respectively). GBR 830 (now called ISB 830) is in a phase 2b clinical trial in atopic dermatitis [70].

Anti-IL-22 Therapy

While atopic dermatitis is often simplistically considered a Th2-mediated inflammatory disease, overexpression of Th17-pathway cytokines plays an important role in the disease, with IL-22 levels corresponding with disease severity [11, 12]. Fezakinumab is an anti-IL-22 monoclonal antibody being investigated for use in atopic dermatitis. In a phase 2a placebo-controlled trial, fezakinumab was investigated in adults with uncontrolled atopic dermatitis for 20 weeks, with dosing of 600 mg at baseline, followed by 300 mg every 2 weeks until week 10 [71]. Compared with placebo, subjects in the fezakinumab arm had significantly greater decline from baseline in SCORAD during weeks 6 through 10. However, the primary endpoint of significantly greater decrease in SCORAD from baseline at week 12 was not achieved. Secondary endpoints of SCORAD50 and SCORAD75 (proportion of patients achieving SCORAD improvements of $\geq 75\%$) responses also did not show statistically significant difference compared with placebo. At 12 weeks, improvement in body surface area involvement was significantly greater in the fezakinumab-treated than in placebo-treated subjects. Several endpoints showed statistical significance when just a severe AD (baseline SCORAD ≥ 50) subpopulation was examined.

Anti-IL-31 Therapy

IL-31 is produced by T cells and has been shown to be an important mediator of itch in atopic dermatitis, through binding of the IL-31A receptor is located on sensory neurons in skin [72]. IL-31 may also be implicated in the disruption of the physical skin barrier in atopic dermatitis [73]. Nemolizumab, an anti-IL-31 receptor α antibody, has shown promise in atopic dermatitis clinical trials to date. Monthly injections of nemolizumab significantly inhibited pruritus in patients with moderate-to-severe AD in a 12-week phase 2 clinical trial [74]. Three doses of nemolizumab (0.1 mg/kg, 0.5 mg/kg, or 2 mg/kg every 4 weeks) achieved a primary endpoint of significantly reducing itch on a pruritus visual analog scale (VAS), when compared with placebo. The 0.5 mg/kg and 2 mg/kg monthly dosing arms also significantly increased improvement in EASI, SCORAD, and sleep disturbance scores compared with placebo.

A 52-week double blind extension of the above trial evaluated the long-term efficacy and safety of nemolizumab subcutaneously at 0.1 mg/kg, 0.5 mg/kg, or 2 mg/kg every 4 weeks or at 2 mg/kg every 8 weeks [75]. At all doses, improvement in pruritus VAS over baseline was maintained or increased from week 12 to week 64, as were improvements in EASI, SCORAD, and sleep disturbance scores. Overall, nemolizumab was well tolerated over 64 weeks in the phase 2 trial. Common treatment-related adverse events described in the phase 2 trials included exacerbation of AD, upper respiratory tract infection, nasopharyngitis, peripheral edema, increased blood creatine phosphokinase level, and injection-site reactions.

A follow-up phase 2b trial has been completed to determine the optimal dose and duration of therapy of nemolizumab [76]. The trial was conducted in patients with moderate to severe AD and severe AD-associated pruritus uncontrolled by topical treatments. A loading dose of 20, 60, or 90 mg was given on day 1, followed by 10, 30, or 90 mg subcutaneous dose every 4 weeks until week 20, with a 12-week follow-up period until week 32. The results of this randomized, double-blind, placebo-controlled trial evaluating three fixed doses of nemolizumab subcutaneous treatment found maximal benefit with the 30 mg dose. The primary endpoint was percent change from baseline in EASI score at 24 weeks. At all doses, nemolizumab showed greater improvement in mean percentage in EASI score at 24 weeks than placebo. The greatest difference from baseline was seen with the 30 mg maintenance dose. Significant difference was also seen at 16 weeks, which is the time point used in most other clinical trials of new therapies in patients with AD. Regarding secondary endpoints, the 30 mg dose was also superior to placebo for IGA score at weeks 4 through 20, though not at week 24. At week 2 and beyond, peak pruritus numerical rating scale scores were greater for all nemolizumab dosing arms.

compared with placebo, with the most marked effects on pruritus scores seen in the 30 mg nemolizumab arm (67.3% vs 35.8% for placebo at week 24, $p < .001$). Recruitment is ongoing for phase 3 clinical trials of nemolizumab in adult and adolescents with moderate-to-severe AD [77, 78].

Anti-IL-12/23 Therapy

Ustekinumab is an IL-12/IL-23p40 antagonist targeting a common subunit (p40) shared by the IL-12 and IL-23 cytokines. It suppresses Th1, Th17, and Th22 activation, and is FDA-approved for use in psoriasis. It has been trialed in adult chronic atopic dermatitis, but studies have failed to demonstrate efficacy. In a phase 2, placebo-controlled, double-blinded, single-center clinical trial, 33 patients suffering from moderate-to-severe atopic dermatitis were treated with either ustekinumab or placebo, and then underwent a crossover to the other arm of therapy after 16 weeks. The primary endpoint was SCORAD50 at 16 weeks (proportion of participants who achieved 50% improvement from baseline in SCORAD). Slightly higher SCORAD50 in the ustekinumab group compared with placebo were found at week 12, 16, and 20 weeks, but this was not statistically significant [11]. Despite the lack of significant clinical effect compared with placebo, after 4 weeks on therapy, the initial ustekinumab arm experienced a marked downregulation of genes related to Th1, Th17, Th22, and Th2-mediated inflammation compared with placebo.

Ustekinumab has also been investigated in adult Japanese patients with atopic dermatitis. The T cell phenotype of atopic dermatitis skin in Asian patients has been found to be different from the inflammatory composition of the atopic dermatitis microenvironment in patients of other ethnicities. Patients of Asian background with atopic dermatitis have more predominant Th17 and Th22 responses compared with patients with atopic dermatitis of European descent [79]. However, ustekinumab, with its effects on Th1-, Th17-, and Th22-mediated inflammation, failed to show efficacy in a Phase 2 trial in Japanese patients with severe atopic dermatitis [80]. This study was a placebo-controlled trial of two doses of ustekinumab, either 90 mg or 45 mg $\times$ 2 doses, 4 weeks apart. Both treatment arms failed in the primary endpoint; they showed non-significant improvement in EASI score compared with placebo. In addition, non-significant improvement in several major secondary endpoints was observed in both ustekinumab groups versus placebo.

Risankizumab is a humanized IgG monoclonal antibody against IL-23 specifically. It is also FDA-approved for treatment of psoriasis, and is currently in phase 2 clinical trials for use in atopic dermatitis [81].

Approaching the Treatment of Severe Atopic Dermatitis in the Biologic Era

The array of upcoming biologic treatment options for severe refractory atopic dermatitis is promising. In the interim, the treatment of severe refractory disease will continue to be challenging, especially in the pediatric population for which studies are lacking. Guidelines for atopic dermatitis treatment from the American Academy of Dermatology and the Joint Task Force on Practice Parameters for Allergy and Immunology provide useful evidence-based therapeutic approaches [14, 82, 83]. Phototherapy is a well-established second-line treatment for eligible children and adults; however, its use is limited by availability and patient and family concerns regarding side effects. When phototherapy is not an option, dupilumab is an attractive choice for maintenance treatment of moderate to severe disease for adolescents and adults, and now for ages 6 to 11 years following recent FDA approval for use in this age group [50].

As has become the case with asthma, clinicians will soon have a variety of biologics to choose from for the treatment of atopic dermatitis. One can foresee the dilemma will then become how to choose from available options. Phenotyping atopic dermatitis subtypes to determine the best biological target for individual patients is an aspirational approach to guide treatment decisions when several biologics become available, but advances in the understanding atopic dermatitis pathologies and the development of biomarkers will be required for this approach to be optimized. Pragmatic issues such as availability based on payer preference, physician familiarity, comorbidity, and tolerability will be important factors informing the choice among multiple biologics. For the specialist with several options available, more nuanced approaches may take into account primary endpoints studied in phase 3 clinical trials. Comparing primary endpoints that rate the severity and extent of lesional skin may be helpful in choosing a preferred agent, though lack of head-to-head studies will limit the conclusions that may be drawn from such comparisons. Clinicians may also consider studies that report on subjective symptoms such as sleeplessness or pruritus, and elect to use agents that show benefit in these outcomes for their patients who report these symptoms to be most bothersome.

Conclusion

In a complex inflammatory disease such as atopic dermatitis, there are many potential immunologic targets for biologic therapies. While skin care and topical therapies control most cases of atopic dermatitis, there are pediatric and adult patients with difficult-to-treat eczema who require systemic therapies to manage their disease. Targeted biologic therapies offer the

potential if safer, effective systemic therapies, compared with the off-label use of immunosuppressants which have been a mainstay of treatment for severe uncontrolled atopic dermatitis until just recently. Unfortunately, the armamentarium of FDA-approved targeted biological therapies remains limited at present. Several promising candidates have failed in clinical trials, and while dupilumab offers significant benefit to many patients with severe atopic dermatitis, additional monoclonal antibodies in the therapeutic pipeline are anticipated to soon offer valuable alternatives for these patients. Of course, beyond the short-term efficacy to be demonstrated in initial clinical trials, long-term follow-up studies examining persistence of effect of each therapy will be important for those dealing with chronic atopic dermatitis.

In addition to the monoclonal antibodies addressed in this review, various small molecule therapeutics are being evaluated for atopic dermatitis. These included Janus Kinase inhibitors (JAKinibs) and histamine H4 receptor antagonists. In the future, having several of the above treatment options addressing different contributors within the atopic dermatitis inflammatory microenvironment in the physician's armamentarium will allow for treatment of some of the most challenging cases of atopic dermatitis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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