



Biologics for Allergic Dermatologic Diseases

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Abstract

Purpose of Review Atopic dermatitis (AD), chronic spontaneous urticaria (CSU), and allergic contact dermatitis (ACD) represent three important allergic dermatoses with many unmet therapeutic needs. The development of biologic agents has opened the door to both new treatment options and improved understanding of the underlying pathophysiology, both shared and unique for these entities. With several FDA-approved medications available and many more in development, the biologic revolution has begun for allergic dermatoses.

Recent Findings This is a narrative review on the current state of pathomechanisms and appropriately targeted biologic agents for these three common allergic skin conditions. The importance of Th2 inflammation and the effect of inflammatory cytokines on the skin barrier may help explain the impressive efficacy of biologic agents, while maintaining relative safety. While some of the biologic agents show efficacy across multiple allergic dermatoses, more often it seems these more targeted pathways show accordingly precise efficacy. However, in each disease, multiple agents hold promise, and may be differentiated by safety and adverse effect profile rather than simply by efficacy.

Summary New understanding of the pathogenesis of the allergic dermatoses has ushered in a new era of biologic therapies. Competing mechanisms and molecules will continue to be developed and vetted in trials with hopes of continuously refined precision therapies with optimized safety and efficacy profiles.

Keywords Biologics · Atopic dermatitis · Urticaria · Allergic contact dermatitis · Treatment

Introduction

Atopic dermatitis (AD) stands as the paragon of allergic skin disease. It represents a chronic pruritic condition that burdens children and adults, often with refractory symptoms and significant personal, social, and financial costs. It is estimated that 16.5 million adults and 9.6 million children suffer from AD in the USA alone [1•, 2]. The quality of life of sufferers is significantly impaired as evidenced by the higher prevalence of sleep disturbances, depression, and anxiety compared with the general population [3]. A 2006 report found the total annual burden of AD was \$4.228 billion (in 2004 USD), which was the equivalent of \$5.297 billion in 2015 [4].

Although the pathogenesis of AD is not completely understood, both genetic and environmental factors have been implicated. While its pathophysiology is clearly multifactorial, a central aspect is skin barrier dysfunction [5]. Filaggrin, an important structural protein for the skin barrier, plays a crucial role in preventing dehydration and pH alterations in the skin. Loss-of-function mutations in the *FLG* gene, which codes for filaggrin, interrupt the keratin filaments in AD and allow increased transepidermal water loss (TEWL) [6].

Recent studies have emphasized IL-4 and IL-13 as primary Th2 cytokines stimulating the “atopy” of AD, as evidenced by the increased expression of precursors to Th2 cytokines in acute AD lesions [7]. Additionally, both IL-4 and IL-13 have been found to inhibit the mRNA necessary for *FLG* synthesis and therefore disrupt proper filaggrin development, with important skin barrier ramifications [8].

These pathological processes compounded with environmental threats such as skin microbiome disruption, pollutant exposure, temperature variation, and a myriad of other skin barrier disruptors cause a wide array of AD presentations and severities. The identification of the inflammatory pathways

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underpinning AD has been the nidus for the first monoclonal antibody for its treatment [5].

Closely related to AD from a morphological standpoint, and often present as secondary diagnosis, allergic contact dermatitis also results in eczematous patches and plaques. Allergic contact dermatitis (ACD) is often in the differential diagnosis for AD and can be similar in its presentation, but has an environmental trigger and should resolve once the allergen is removed [9]. ACD is a type IV cutaneous cell-mediated hypersensitivity reaction triggered by environmental allergens, binding to carrier proteins and forming complexes, which elicit an inflammatory response [10]. Upon subsequent exposure to the allergen, sensitized T cells release inflammatory mediators and cause epidermal spongiosis [11, 12].

ACD is a significant occupational hazard: the National Occupational Research Agenda (NORA) has estimated an annual cost of at least \$1 billion associated with contact dermatitis, due largely to absenteeism and loss of productivity [13]. The burden of disease on individual patients goes far beyond cost, with many facing job transfers or unemployment [14]. While AD and ACD may present similarly, a thorough clinical history and patch testing when necessary can usually distinguish between the two and guide therapeutic options.

Finally, chronic spontaneous urticaria (CSU) relies on an IgE-mediated pathway to round out the last of the major allergic dermatoses. Urticaria is a common, mast cell-driven condition characterized by the rapid onset of wheals and/or angioedema, sometimes with a clear trigger, such as infections, food or drug intolerances, or autoimmunity [15, 16]. Among inflammatory mediators synthesized by mast cells, IL-4 and IL-5 stand out as they are also implicated in the pathogenesis of AD [17].

Urticaria compromises health-related quality of life in many patients due to the uncomfortable and debilitating symptoms that exacerbate psychiatric morbidity. CSU patients have significantly higher rates of hypochondriasis, depression, paranoia, and social introversion ($p < 0.05$) [18].

All three of these common allergic dermatoses pose significant therapeutic challenges and have many unmet needs. The armamentarium of conventional therapies often falls short, especially in moderate or severe cases. Moreover, many of the classical systemic medications used for these conditions have a host of serious side effects that make them even less desirable [19]. The wide gamut of therapies can be explained by the variability in presentation and severity, and possibly by the insightful axiom: "In general, successful treatment of any disease is probably inversely related to the number of recommended regimens." [20].

Historically, most treatments are considered reactive, addressing clinical symptoms without targeting the pathways that initiate the disease. Biologics are promising due to their specificity in targeting the underlying disease mediators, demonstrated by their relative safety and significant success in

many diseases. Here, we review the current biologic agents available and actively being studied for allergic dermatoses, with an understanding that the pipeline is quite robust and new agents may soon alter this rapidly changing area.

Biologic Agents

The focus of this review will be on biologics targeting cytokines that antagonize processes behind atopic and other skin conditions. There are 3 general mechanisms by which biologics interfere with pathological pathways: soluble receptors, antibodies against cytokines themselves, and antibodies against cytokine receptors.

Soluble receptors exert their function by maintaining a high affinity for their cytokine ligand and thus bind and sequester it in circulation. For example, etanercept, a soluble TNF- α receptor fusion protein, binds trimeric TNF- α and sequesters it, inhibiting the inflammatory processes of certain rheumatologic diseases [21, 22].

Anti-cytokine antibodies are currently the most widely used approach. These antibodies capture their specific cytokine and prevent it from binding to its receptor thus inhibiting the biological consequences of the cytokine's actions. The efficacy of anti-cytokine antibodies, however, is variable depending on the source, targets, immunoglobulin subclass, glycosylation, and allotype of the antibodies [21].

Many antibodies for clinical use are either humanized, meaning they are derived from non-human organisms and modified to increase their similarity to human variants, or fully human, meaning they are derived from human immunoglobulin genes. Humanization of murine monoclonal antibodies improves their tolerability in patients, but the current therapeutic frontrunner is fully human-derived antibodies with pre-selected antigen specificity in vivo by genetically modified mice or by antibody engineering processes [23]. Fully human and humanized antibodies appear to be safer therapeutic options as they are less likely than murine or chimeric antibodies to cause undesirable immune responses [24].

Finally, anti-receptor antibodies exert their biological activity by acting as a competitive inhibitor of the receptors and inhibiting the natural ligand from binding. Theoretically, anti-receptor antibodies have the potential to confer greater efficacy due to their ability to affect their circulating cellular targets before entering inflamed tissues, whereas anti-cytokine antibodies are limited by their inability to penetrate the inflammatory space where cytokines are acting [21]. (See Table 1).

Anti-IgE Therapy

While the role of IgE in atopic diseases has not been fully elucidated, it is clearly a central factor [25]. Omalizumab, a

Table 1 Biologic agents in allergic dermatoses

	Drug	Target mediator	Indications	Use in allergic dermatologic diseases	Notes
Anti-IgE therapy	Omalizumab	IgE	Severe asthma (≥ 6 years), CSU	Unreliable efficacy in AD [27–30]. Approved for CSU refractory to antihistamines (≥ 12 years) [32•]	Anti-IgE monoclonal antibody
	Ligelizumab	CD20		Under investigation for AD therapy [34]. Potentially superior to omalizumab in treating CSU [34]	
T cell response interruption	Efalizumab* Alefacept*	CD11a CD2	Psoriasis Psoriasis	Some value in AD therapy, but pulled from market Some value in AD therapy, but pulled from market	Inhibits T cell activation by blocking receptor-ligand interaction
Targeting B cells	Rituximab	CD20	Hematologic conditions	Significant anti-inflammatory effect in AD [38]. Some improvement in refractory CSU [39]	Anti-CD20 antibody
Inhibition of Th2 response	Mepolizumab	IL-5	Severe eosinophilic asthma (≥ 6 years)	Clinically insignificant symptom relief in AD [45–47]	Anti IL-5 monoclonal antibody
	Nemolizumab	IL-31		Rapid, sustained pruritus relief, significant improvement in EASI and NRS-itch scores in AD [58, 59•]	Anti IL-31Ra monoclonal antibody Granted Breakthrough Therapy Designation by FDA
	Fezakinumab	IL-22		Significant improvements in SCORAD, IGA [63]	Anti IL-22 antibody
	Ustekinumab	IL-12, IL-23	IBD, psoriasis, psoriatic arthritis	Insignificant improvements in severe AD [67]	Anti-p40 subunit of IL-12 and IL-23 monoclonal antibody
	Dupilumab	IL-4, IL-13	Moderate-severe AD (≥ 12 years), moderate-severe asthma, chronic rhinosinusitis with nasal polyposis	Significant improvements in AD pruritus and QoL in adults [80•]. Significant symptom improvement in adolescents (12–17 years), no new safety concerns [85]. Concluding phase 3 trials for infants ≥ 6 months, children, moderate-severe AD [87]	Anti IL-4Ra monoclonal antibody. Currently the only FDA approved biologic for AD
	Lebrikizumab	IL-13		Significant improvement in AD, good safety profile [98••]	Anti IL-13 monoclonal antibody
	Tralokinumab	IL-13		Significant improvements in EASI, IGA, SCORAD, DLQI, and pruritus observed in AD [100••]	Anti IL-13 monoclonal antibody
Anti-thymic stromal lymphopoietin therapy	Tezepelumab	TSLP		Insignificant improvement in EASI in AD [103]	Anti-TSLP IgG2A monoclonal antibody

AD atopic dermatitis, ACD allergic contact dermatitis, CSU chronic spontaneous urticaria, QoL quality of life, EASI Eczema Area and Severity Index, IGA Investigator's Global Assessment, SCORAD Scoring Atopic Dermatitis DLQI

*No longer available

humanized IgG1 monoclonal antibody against IgE, has been tested in patients with severe asthma and chronic idiopathic urticaria successfully and is FDA approved for both of these indications [26]. Despite some positive reports, omalizumab has not had reliable clinical efficacy in patients with AD [27–30]. This may be due to very high levels of IgE in AD patients compared with asthmatics. Alternatively, IgE may simply not play as central a role in AD and thus would not provide a robust clinical effect [26]. Furthermore, little is known about omalizumab's role in treating ACD, with only one successfully treated case of occupational wheat contact dermatitis indicating omalizumab's efficacy [31].

Omalizumab is the only non-antihistamine drug approved for the treatment of CSU based on the fact that IgE and its receptor FcεRI are important in urticarial pathogenesis [32•]. However, ligelizumab, a new high-affinity humanized monoclonal antibody against IgE, has shown dose-dependent and

time-dependent suppression of IgE superior to that observed with omalizumab [33]. When administered to patients with CSU for 12 weeks, a significant (CI = 0.95) percentage experienced complete control of their symptoms, regardless of dose. Of importance, the ligelizumab group outperformed the omalizumab and placebo groups. Ligelizumab is currently also under investigation for the treatment of AD [34].

Interrupting T Cell Response Pathway

T cell responses play a significant role in inflammation. Efalizumab and alefacept are biologics that inhibit T cells by blocking the receptor-ligand interaction that activates T cell responses. Both demonstrated improved clinical symptoms in AD patients [35, 36], but have been pulled from the market due to serious adverse events [26].

Targeting B Cells

Alternatively, targeting an upstream activator of the T cell response may have a similar effect. CD20 is a B lymphocyte antigen that promotes the natural differentiation of B cells and plays a crucial role in the development of humoral immunity. Specialized antigen presenting by B cells contributes to activation and amplification of T cell responses. Since Th2 cells play a significant role in AD, the disruption of their activation by B cells could provide relief for AD patients [37]. Rituximab, an anti-CD20 antibody currently indicated for hematologic disorders, provided a significant ($p < 0.001$), rapid, and sustained decrease in skin inflammation when tested with AD patients [38]. Rituximab has also been reported to improve cases of CSU refractory to antihistamines, omalizumab, and immunosuppressants in as early as 1 week after treatment initiation [39]. While this is not enough data to recommend rituximab for these conditions directly, it does indicate that inhibition of CD20 deserves further investigation as a potential therapeutic pathway in allergic dermatoses.

Inhibition of Th2 Responses

Acute AD lesions are characterized by profound increases in Th2 levels and therefore a surge of Th2-produced cytokines: IL-4, IL-5, IL-13, IL-31 [40]. The overabundance of these interleukins can wreak havoc on the immune system. Beyond inflammation, these mediators have been associated with the downregulation of terminal differentiation genes and tight junction products, both of which are essential for barrier integrity of the skin and are compromised in AD patients [41]. Antibody-mediated inhibition of any of these interleukins may hinder the Th2 pathway enough to inhibit the pathogenesis of AD.

Anti IL-5 Antibody

Mepolizumab, a humanized IgG monoclonal antibody, binds IL-5, which is responsible for the activation, growth, and differentiation of eosinophils [42]. Eosinophils are major directors of inflammatory processes in allergic diseases and it has been demonstrated that knockout mice lacking IL-5 experience less skin eosinophilia and epidermal thickening when exposed to allergens [43]. In humans, mepolizumab was found to reduce baseline blood eosinophil counts, pointing to potential for IL-5 inhibition to treat AD [44]. In a randomized placebo-controlled trial for AD, patients saw significant reductions ($p < 0.05$) in peripheral blood eosinophil levels, but only modest improvements in symptoms and no notable improvement in dermatitis or pruritus. The study concluded that two doses of 750 mg mepolizumab did not provide clinical benefit for patients, but could not determine if a higher dose or

longer duration would reduce signs and symptoms of AD [45].

A similar multicenter trial treated adult patients with moderate-to-severe AD with 100 mg subcutaneous mepolizumab or placebo every 4 weeks for 16 weeks. Again, results did not show significant clinical improvement in patients with moderate-to-severe AD but did demonstrate a reduction in blood eosinophil levels. This suggests that blood eosinophils may have negligible impact on tissue-bound eosinophils relevant in AD and that anti IL-5 therapy may be ineffective in AD [46, 47].

Mepolizumab, along with anti IL-5 antibodies reslizumab and benralizumab, have not been well studied in CSU or ACD. Case reports have described dramatic and sustained improvements in CSU symptoms and infection-triggered flares, but further investigation is needed to make solid conclusions on efficacy [48–50].

Anti IL-31 Strategies

IL-31 is a cytokine produced by Th2 lymphocytes that contributes to the pruritus of AD as modeled by the AD-like disease caused by IL-31 expression in mice [51]. In humans, numerous studies have observed enhanced expression of IL-31-encoding genes in skin lesions of AD patients [52]. In AD, IL-31 mRNA is overexpressed in both lesional and non-lesional skin [53], and there appears to be a correlation between serum IL-31 levels and phenotypic severity [54, 55]. Moreover, patients with AD may be more sensitive to circulating IL-31 as it has been shown that their keratinocytes have higher IL-31 receptor alpha (IL-31RA) expression [52]. All of these findings suggest IL-31 has a role in AD.

One key finding is that IL-31 interferes with keratinocyte proliferation and differentiation and suppresses filaggrin expression [56]. Developing biologics to target IL-31 is particularly intriguing, as it has the potential to disrupt the pathogenesis of AD in any or all of these pathways.

Nemolizumab is a monoclonal antibody against IL-31RA. Clinical efficacy has been shown as early as 2017 [57]. A phase 2b randomized-controlled trial found that 30 mg subcutaneous injections of nemolizumab every 4 weeks for 24 weeks significantly improved EASI ($p = 0.016$) and/or NRS-itch scores ($p \leq 0.01$). Of importance, nemolizumab improved inflammation and provided rapid and sustained pruritus relief with an acceptable safety profile [58]. The prurigo lesions seem to respond especially well [59]. With these results, nemolizumab has been granted Breakthrough Therapy Designation from the FDA as it may be a superior treatment to current therapeutic options for the pruritus of AD [60]. As there appear to be increased levels of IL-31 in CSU and ACD as well, nemolizumab may also have an effect in these conditions, although it has not yet been studied [61, 62].

Anti IL-22 Antibody

Key characteristics of AD are a compromised skin barrier with epidermal hyperplasia and abnormal keratinocyte differentiation accompanied by activation of Th2 and Th22 pathways. Early animal studies suggest IL-22 plays a major role in the Th22 pathway, promoting hyperplasia and inhibiting keratinocyte differentiation and skin barrier formation [63]. Mice models engineered to overexpress IL-22 in the skin demonstrate a chronic AD phenotype with pruritus, enhanced Th2 immunity, and a “leaky” skin barrier [64]. Thus, IL-22 is a potential driver of AD and biologics targeting IL-22 could provide therapeutic benefit.

Fezakinumab is a human monoclonal antibody being developed for the treatment of psoriasis and rheumatoid arthritis by targeting IL-22. In a study examining the efficacy and safety of fezakinumab in patients with severe AD, treatment resulted in consistent improvements in clinical and molecular disease scores as compared with placebo after just 12 weeks (SCORAD, $p = 0.029$; IGA, $p = 0.034$). Improvements in all outcome measures were sustained until week 20, 10 weeks after the last dose ($p = 0.01$). Fezakinumab also showed a favorable safety profile, holding promise as another potential therapeutic option [63].

Anti IL-12 and IL-23 Antibody

Ustekinumab, a fully human monoclonal antibody against the p40 subunit of IL-12 and IL-23, is currently approved for the treatment of inflammatory bowel disease, psoriasis, and psoriatic arthritis. In the skin, IL-12 plays a role in promoting the differentiation of Th1 cells, and IL-23 stimulates the proliferation and survival of Th17, which is responsible for the production of various inflammatory cytokines [65]. Therefore, downregulation of IL-12 and IL-23 is a potential target for the control of AD. While case studies have reported positive results in patients with refractory AD [66], the results from a phase 2 trial did not show clinically meaningful differences in patients with severe AD [67]. It is unclear if further development for AD or other allergic dermatoses will be undertaken.

Anti IL-4 and IL-13 Strategies

IL-4 and IL-13 are homologous cytokines produced by Th2 lymphocytes and are central to the pathogenesis of allergic diseases and asthma. Both cytokines have increased expression in AD patients and are pro-inflammatory as well as having detrimental effects on the skin barrier [68, 69].

IL-4 and IL-13 inhibit filaggrin production during keratinocyte differentiation and downregulate loricrin and involucrin, proteins crucial for skin barrier integrity [70, 71]. A compromised skin barrier allows for bacterial and allergen

penetration increasing the risk of infection and allergic sensitization, both common in AD [71]. Furthermore, skin colonization by *Staphylococcus aureus* is common in AD and may be promoted by antimicrobial peptide (AMP) suppression by IL-4 and IL-13 [72, 73]. Patients can often be caught in a cycle of infection with exacerbated skin inflammation and barrier dysfunction, allowing *S. aureus* to perpetuate [73].

IL-4 and IL-13 may facilitate hypersensitivity reactions by promoting IgE production from plasma cells, leading to inflammation in skin and blood [74, 75]. Moreover, IL-4 has been implicated in promoting IL-31 production and worsening inflammation manifested as pruritus [76]. Of interest, IL-4 and IL-13 share signal transduction pathways in addition to their cytokine functions, which has made them useful targets for therapy [77]. The binding of IL-4 or IL-13 to the IL-4 receptor (IL-4R) and the subsequent STAT6 activation has been shown to amplify the IL-4R signal transduction cascade and shift CD4⁺ T cell differentiation toward Th2 lineage [78]. The IL-4R α subunit of the receptor is the target of fully human monoclonal antibody dupilumab [79].

In two phase 3 studies in which dupilumab monotherapy was compared with placebo at 16 weeks, dupilumab resulted in a clear or almost clear global assessment in 38% versus 10% of the placebo ($p < 0.001$) in the first, and 36% versus 8% of placebo ($p < 0.001$) for the second. The dupilumab groups also had improvements in pruritus ($p < 0.0001$), symptoms of anxiety or depression ($p < 0.05$), and quality of life ($p < 0.05$) over placebo [80••]. The success of dupilumab in these studies points to the central role of IL-4 and IL-13 in allergic disease settings.

In an effort to further assess the safety profile of dupilumab, the LIBERTY AD CHRONOS study assessed patients for 52 weeks of continuous treatment (dupilumab every week + TCS, every 2 weeks + TCS, or placebo). Results were similar to those found in other studies, with significantly more patients receiving dupilumab plus corticosteroid achieving the primary endpoint of IGA score 0 or 1 ($p < 0.0001$). Patients using dupilumab also experienced reduced flare rates and decreased use of rescue treatments including corticosteroids and systemic immunosuppressants [81].

Serious adverse events were reported in 4% of patients who received dupilumab at 2-week intervals, and 5% of patients who received placebo. There were no significant dupilumab-induced laboratory abnormalities, and consequently there is no need for laboratory testing during treatment [82••]. The most common adverse effects were injection site reactions and conjunctivitis, with 15% of those treated with weekly dupilumab experiencing injection site reactions and 14% experiencing conjunctivitis in the 52-week trial [81].

While conjunctivitis incidence is increased in dupilumab-treated AD patients, the same was not seen in those being treated with dupilumab for asthma or nasal polyposis [83, 84]. It remains unclear why this side effect would be disease specific, especially given the fairly significant overlap

between these disorders. Nonetheless, the increased risk of conjunctivitis with dupilumab usage must be considered when evaluating therapeutic options at least in AD.

The robust improvements observed in these studies are encouraging for AD therapy in adults. However, children are some of the most heavily burdened AD patients, with similar quality of life challenges as adults compounded with the responsibility of regimented therapies, restrictions on activities, and social repercussions of visible disease.

A phase 3 study assessed dupilumab use in adolescents (≥ 12 years) with moderate-to-severe AD and found support for its use in this population. No new safety concerns were observed for the adolescent population [85]. In 2019, dupilumab was FDA approved for the treatment of moderate-to-severe uncontrolled AD in ages 12–17 years, with a new dosing regimen for those under 60 kg: 400 mg loading dose, followed by 200 mg every 2 weeks [86].

Recent results of a phase 3 trial of dupilumab in children aged 6–11 years with severe AD were announced (though not yet published in a peer-reviewed journal), and demonstrated that adding dupilumab to topical corticosteroids greatly improved disease severity, skin clearing, itching, and AD-related quality of life [87]. Trials of dupilumab in children 6 months to 5 years of age are ongoing ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03346434) identifier NCT03346434) [88, 89].

Importantly, dupilumab has not received FDA approval for use in children under 12 years at this time. Current off-label use of dupilumab for children is limited by only being available in 2 doses: 200 mg and 300 mg syringes. A case series of patients under age 18 receiving dupilumab suggested that it may be an effective treatment option for younger patients and could be considered for some children prior to FDA approval [90]. This was corroborated by a recent multicenter review [91].

There is sparse data on dupilumab's role in treating ACD, but a case series of patients with severe, refractory ACD showed promising results with major improvements in pruritus and quality of sleep [92]. Confusingly, however, patch testing for ACD while on dupilumab appears to be possible with only minor loss of sensitivity [93]. One recent paper suggests that the inhibitory effect may be allergen specific, perhaps allowing for reconciliation of these seemingly contradictory findings [94].

Dupilumab's inhibition of IL-4 and IL-13 signaling and IgE production may be beneficial for CSU patients as well. A case study of 6 patients with CSU that were unresponsive to omalizumab responded well to dupilumab, which has led to ongoing studies evaluating safety and efficacy of dupilumab in CSU patients [95].

Anti IL-13 Antibody

While dupilumab treats AD by targeting IL-4 and IL-13, an antibody against solely IL-13 may also provide therapeutic

benefit [96]. Lebrikizumab is a humanized monoclonal antibody with high affinity for soluble IL-13 [97]. Lebrikizumab proved to be superior to placebo ($p = 0.026$) in a study of 209 patients with AD when administered subcutaneously every 4 weeks along with topical corticosteroids. During the 12-week treatment period, response curves trended upward in the final weeks suggesting the response plateau was not reached in 12 weeks. Lebrikizumab was well tolerated with relatively few adverse events, the most notable being 9.6% of the lebrikizumab groups (pooled) experiencing conjunctivitis compared with 7.5% in the placebo group [98••].

Tralokinumab is a fully human monoclonal antibody that also binds to and neutralizes IL-13 [99]. A phase 2b study of 204 adults with moderate-to-severe AD was conducted with concomitant topical steroid use. At the 12-week endpoint, 300 mg of tralokinumab significantly improved EASI score versus placebo ($p = 0.1$) and 26.7% reached an IGA response of 0 or 1 versus 11.8% of the placebo group [100••]. Improvements in SCORAD, Dermatology Life Quality Index, and pruritus were also noted to be greater than placebo. Adverse events included upper respiratory tract infections and injection site reactions, but notably there were no cases of conjunctivitis reported in the 300 mg group (and a 2.6% rate in aggregate across all dose groups) compared with 3.9% of participants in the placebo group [100].

While further data is required given these relatively small phase 2 trials, these two drugs support the notion that targeting IL-13 in patients with AD has significant therapeutic potential.

Anti-thymic Stromal Lymphopoietin Monoclonal Antibody

Thymic stromal lymphopoietin (TSLP) is a cytokine first isolated from murine thymic stromal cells. Its role in immunology is illustrated by the fact that when TSLP dendritic cells (TSLP-DCs) are used to stimulate CD4⁺ T cells in vitro, they induce Th2 cells to produce IL-4, IL-5, IL-13, and TNF- α , classic inflammatory cytokines [101, 102]. TSLP is highly expressed by keratinocytes of skin lesions in human AD and may serve as a regulator of allergic inflammation.

Tezepelumab is a fully human IgG2 λ monoclonal antibody that binds TSLP and prevents it from interacting with its receptor. When administered to patients with AD, a greater percentage of patients achieved EASI50 versus placebo ($p = 0.91$). The results were not statistically significant, however, and tezepelumab requires further studies before it can be deemed a therapeutic option [103]. Similarly, TSLP has been implicated in the pathogenesis of CSU, as it initiates type 2 immunity and serum TSLP levels are often elevated in CSU patients [104]. Thus TSLP remains a prime target for drug therapy and tezepelumab holds promise to more effectively treat CSU, although it has not yet been studied.

Conclusion

The dynamic and increasingly nuanced understanding of allergic dermatoses and their commonalities lends itself to new therapeutic opportunities. As biologic therapies continue to gain momentum in this arena, it underscores the importance of conceptualizing these conditions as true systemic diseases with far-reaching physical, social, and psychological consequences.

While dupilumab has quickly become the forerunner of biologic therapy for AD and omalizumab for CSU, other agents in an increasingly robust pipeline may soon become tangible options. This is a new, exciting era in allergic dermatologic therapeutics, with highly effective drugs with low toxicity and the potential for greater patient compliance and satisfaction.

Compliance with Ethical Standards

Conflict of Interest Dr. Bilimoria reports a grant from the National Eczema Association during the conduct of the study. Dr. Lio reports personal fees from UCB, personal fees from Dermavant, grants and personal fees from Regeneron/Sanofi Genzyme, personal fees from Dermira, personal fees from Pfizer, personal fees from LEO Pharmaceuticals, grants and personal fees from AbbVie, personal fees from Kiniksa, personal fees from Eli Lilly, during the conduct of the study; personal fees from La Roche Posay/L'Oreal, personal fees from Pierre-Fabre, personal fees from Johnson & Johnson, personal fees from Unilever, personal fees from Menlo Therapeutics, personal fees from Theraplex, personal fees from IntraDerm, personal fees from Exeltis, grants and personal fees from AOBiome, personal fees from Realm Therapeutics, personal fees and other from Franklin Bioscience/Altus Labs, personal fees from Verrica, personal fees from TopMD, personal fees from Arbonne, personal fees from Burt's Bees, grants from the National Eczema Association, outside the submitted work. In addition, Dr. Lio has a patent Theraplex Product with royalties paid and Board member and Scientific Advisory Committee Member of the National Eczema Association.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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