Targeting the T Helper 2 Inflammatory Axis in Atopic Dermatitis

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting up to 25% of children and approximately 10% of adults [1–5]. Although most patients develop AD before the age of 5 years, 9–17% of patients may not develop AD until adulthood [6–8]. For many children, the onset of AD marks the beginning of a progression from AD to food allergy, allergic rhinitis, and eventually asthma, a scenario frequently described as the “atopic march” [9, 10]. On the other hand, many children outgrow their AD before adolescence, indicating that the “atopic march” is not an inevitable course. However, studies focusing on disease onset during infancy and early childhood might overestimate the percentage of children who outgrow their AD if there is not adequate follow-up during the teen years and adulthood [11]. Likewise, asthma and food allergy can disappear as the child grows older [12, 13]. Data on the progression from AD to asthma over the last 3 decades reveal that this phenomenon appears to depend on a variety of factors including early-life wheezing, allergic sensitization, and the sex of the patient [14, 15]. Van der Hulst et al. [16], in their systematic review of prospective cohort studies involving the relationship of early AD to subsequent childhood asthma, observed an increased risk (odds ratio 2.14; 95% confidence interval 1.67–2.75) of developing asthma following early onset AD. More recently, the Prevention of Allergy
among Children in Trondheim study demonstrated an increased risk (odds ratio 3.07; 95% confidence interval 1.79–5.27) of asthma at the age of 6 years in those patients who had developed AD by the age of 2 years [17]. Recently, a genome-wide association study demonstrated a significant overlap between the susceptibility loci for AD and asthma [18], further supporting the link between early-onset AD and asthma [19].

The skin of patients with moderate to severe AD is characterized by widespread lesions, which manifest as erythematous areas with crusting and/or scaling, oozing, excoriations, and lichenification. Pruritus is one of the major symptoms of the disease and may be severe, causing sleep disturbance [20]. Altogether, these symptoms may lead to a profound impact on the patient’s self-esteem and quality of life [21, 22]. The skin is characterized by a predominant T helper 2 (Th2) environment, which, combined with the itching and resulting mechanical disruption of the skin barrier, plays a central role in the pathogenesis of the disease. Most patients with AD present with increased serum immunoglobulin E (IgE) levels, blood eosinophilia, and allergen sensitization, as a result of increased Th2 pathway activation [23]. Chronic AD lesions display a mixed Th1 and Th2 response, and the release of IL-22 from Th17 and Th22 cells in AD skin samples has been reported. Increased levels of IL-22 in chronic AD lesions compared with the levels in acute lesions suggest that a transition from Th17 to Th22 is associated with chronic disease [24]. Therefore, AD might be considered a Th2/Th22-skewed disease, with an additional contribution from Th1 cytokines occurring in the chronic stages [25]. In addition, loss of function mutations in the gene coding for filaggrin (FLG), an important protein involved in skin barrier integrity, have been reported in subsets of patients with AD [26]. FLG mutations have been identified as a strong risk factor for AD, and might lead to a distinct AD endotype, characterized by early-onset AD that is more persistent and often associated with development of asthma, food allergy, and IgE sensitization [27, 28]. However, the majority of patients with AD do not have FLG mutations, and, in these patients, the downregulation of epidermal FLG expression may be caused by several important factors including Th2 skin inflammation and environmental conditions related to pruritus-induced mechanical damage [27]. The mechanisms by which scratching of the skin may lead to decreased FLG expression are not fully understood. It has been proposed that acute barrier changes, such as those resulting from scratching, can disrupt the calcium gradient which exists in normal epidermis. This gradient is characterized by ascending calcium levels from the basal to the granular epidermal layers, and a subsequent decrease across the stratum corneum. Reduced calcium levels in the stratum granulosum due to scratching could then lead to the downregulation of FLG expression [27].

Another important issue is whether secondary FLG deficiency due to Th2 inflammation, environmental stressors such as low humidity, mechanical trauma due to scratching and other factors, is transient or is a permanent event. Evidence for this being a transient effect may come from the investigation of therapies focused on the restoration of FLG expression [29, 30]. A candidate compound, JTC801, which is a 4-aminoquinoline derivative, was able to increase FLG mRNA expression in both a human immortalized keratinocyte cell line and in normal human epidermal keratinocytes. JTC801 also increased expression of FLG in a human skin-equivalent model, and attenuated atopic skin inflammation in mice in vivo [30]. Another compound, a Janus kinase (JAK) inhibitor, JTE-052, induced FLG expression and decreased the development of AD-like lesions in mice [31]. Finally, coal tar (a traditional topical therapeutic agent for AD) was shown to contain polycyclic aromatic hydrocarbons (PAHs), which activate the aryl hydrocarbon receptor (AHR) signaling pathway, increasing the expression of FLG. Enhanced activation of the AHR signaling pathway by deacetylase sirtuin 1 (SIRT1) has also been shown to promote FLG expression in a mouse model [32]. Taken together, these studies indicate that it may be possible to increase FLG expression, suggesting that secondary FLG deficiency may be reversible, with therapeutic implications for patients with AD.

Given its prevalence and impact on the quality of life of patients, effective treatment strategies are needed for patients with moderate to severe AD. Current treatment recommendations include the liberal use of emollients, wet-wrap therapy, vitamin D supplementation, topical calcineurin inhibitors, and topical corticosteroids (TCS) [1, 33, 34]. When moisturizers alone are not sufficient to control the itch and inflammation, TCS are the mainstay of treatment for AD. Although effective, TCS may be associated with adverse effects, including skin atrophy and increased susceptibility to infections, which are directly related to the potency and the duration of use. Judicious use of high-potency preparations of TCS, avoiding thin-skin areas such as the face or skin folds and minimizing the duration of treatment, is critical [33]. Unfortunately, therapy with TCS alone may not be effective for patients with moderate to severe disease [35, 36]. Allergen immunotherapy is now a consideration in selected patients with
AD and Aeroallergen Sensitization [37]. Phototherapy and systemic immunosuppressant therapies including systemic corticosteroids, cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine, may be used in patients with severe disease refractory to conventional therapy; however, these therapies are associated with significant, potentially serious side effects [1, 33, 37, 38].

Novel therapeutic approaches which target the pathways involved in the pathogenesis of AD provide the opportunity for a potentially more effective and less harmful approach to systemic therapy. The number of clinical trials evaluating the novel chemical and biological agents specifically targeting pathways and mechanisms in AD has steadily increased in recent years and may provide options for patients in the near future. In this review, we will discuss therapeutic approaches for targeting the Th2 axis in moderate to severe AD.

Fig. 1. Targeting IL-4- and IL-13-mediated signaling. IL-4 and IL-13 signaling involves both distinct and overlapping receptors, which results in similar downstream pathway activation. IL-4 signals through the type I receptor, comprising the common γ chain and IL-4Ra, and the type II receptor, comprising IL-4Ra and IL-13Ra1. IL-13 predominantly signals through the type II receptor but also binds to the decoy receptor IL-13Ra2 with high affinity. Pitrakinra (mutein protein) specifically binds to IL-4Ra while dupilumab (monoclonal antibody) prevents IL-4 and IL-13 signaling through IL-4Ra. Additionally, lebrikizumab and tralokinumab are monoclonal antibody therapies that specifically target IL-13. By signaling through their respective receptors, both IL-4 and IL-13 activate the JAK/STAT pathway, inducing the transcription of inflammatory mediators. Tofacitinib and baricitinib are chemical compounds which inhibit JAK activation. IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

The Role of Dominant Th2 Cytokines in AD

The Th2 cytokines, IL-4, IL-5, and IL-13, play a central role in the pathogenesis of AD by activating inflammatory pathways in multiple cell types, impairing epidermal barrier structure and function, and inducing allergen sensitization [39].

Studies have previously reported increased IL-4 and IL-13 expression in acute and chronic skin lesions of patients with AD [40–42], and recently demonstrated increased numbers of CD4- and CD8-positive cells in circulation that secrete IL-4 and IL-13 [43]. The critical role of Th2 cells in AD was recently demonstrated in a study by Czarnowicki et al. [44], who found significant expansion of Th2 cell frequencies in cutaneous lymphocyte-associated antigen-positive (CLA+) T cells of adult patients with moderate to severe AD, compared with healthy con-
controls. Interestingly, the study also revealed reduced numbers of CLA+ Th1 cells, compared with healthy controls. The increased frequency of Th2 cells, particularly within the CLA+ T cell population, suggests that these Th2 cells and the cytokines they produce are an integral part of the pathogenesis of moderate to severe AD.

Preclinical studies performed on transgenic mice further illustrate the central role of IL-4 or IL-13 in AD pathogenesis. Transgenic mice overexpressing epidermal IL-4 spontaneously developed signs and symptoms associated with AD, including epidermal thickening and lesion formation, as well as elevated IgE levels [45]. Similarly, transgenic mice expressing IL-13 in the skin developed intense pruritus in addition to increased IgE production, epidermal thickening, and cellular-infiltration characteristics of AD [46]. In a murine model of IL-4, IL-5, and IL-13, investigators further demonstrated a positive correlation between the onset and progression of AD-like disease and the expression of these Th2 cytokines [47]. IL-4 and IL-13 signal through a common receptor, IL-4Ra, a requisite receptor to induce the signal transducer and activator of transcription 6 (STAT6)/JAK signaling cascade (Fig. 1). Mice genetically modified to constitutively express active STAT6 develop AD-like disease that is reversed by antibodies against either IL-4 or IL-13 [48], suggesting that interfering with this pathway could be efficacious in patients with AD.

IL-4 and IL-13 drive the pathogenesis of disease by modulating several key immunological features including the inhibition of integral barrier proteins such as FLG, loricrin, and involucrin, and the destabilization of tight junctions [49–52], leading to the enhanced penetration of allergens and pathogens. Additionally, downstream signaling of IL-4 and IL-13 has been shown to prevent the induction of innate immune response genes, such as β-defensins and cathelicidin [41, 53, 54], thereby increasing the susceptibility of patients to Staphylococcus aureus and herpes simplex virus skin infections [55, 56].

Pitrakinra is a recombinant human IL-4 mutein that specifically binds to IL-4Ra (Fig. 1), thereby inhibiting the downstream signaling of both IL-4 and IL-13 [57]. Initial studies using pitrakinra in asthma demonstrated a positive clinical effect, as demonstrated by reduced airway inflammation [58], prompting further exploration in AD. The therapeutic effect of pitrakinra in AD was evaluated in a phase 2, double-blind, placebo-controlled study (NCT00676884; Table 1) on 25 patients; however, the results from the trial, completed in 2006, have not yet been published. Dupilumab also binds to IL-4Ra, therefore blocking both the IL-4 and IL-13 signaling pathways (Fig. 1). Although these 2 compounds may share the ability to prevent IL-4 and IL-13 signaling, their structures and modes of action are very different. Pitrakinra was developed by creating mutations in the IL-4 molecule, conferring the ability to antagonize the activation of IL4-Ra, whereas dupilumab is a fully human monoclonal antibody that specifically targets IL-4Ra and blocks downstream signaling by preventing the dimerization of IL-4Ra with IL-13Ra1 or the γ chain. In recent years, dupilumab has demonstrated clinical efficacy in multiple phase 1, phase 2, and phase 3 clinical studies in patients with moderate to severe AD (Table 1) [59, 60]. In 2014, Beck et al. [59] reported that weekly treatment with dupilumab monotherapy (300 mg) for 12 weeks reduced skin disease severity, as measured by the Eczema Area Severity Index (EASI), by 74.0%, compared with 23.3% with placebo. Additionally, dupilumab-treated patients observed an almost 60% reduction in the body surface area affected, and 40% of patients achieved disease clearance (Investigator’s Global Assessment score of 0 or 1) at day 85. Furthermore, patients treated with dupilumab experienced significantly fewer skin infections (0.05 infections per patient) than patients treated with placebo (0.20 infections per patient). Usage of TCS in addition to dupilumab provided even greater clinical benefit. Recently, a larger phase 2b clinical trial was conducted to evaluate a dose response and different dosing frequencies of dupilumab. Thaçi et al. [60] confirmed the therapeutic benefit of weekly dosing with 300 mg of dupilumab (−73.7 ± 5.2% change in EASI from baseline), but additionally observed improved skin scores with alternative dosing regimens of 200 mg every other week (−65.4 ± 5.2%), 300 mg every other week (−68.2 ± 5.2%), and 300 mg every 4 weeks (−63.5 ± 4.9%). Skin improvement in each cohort additionally corresponded with a reduction in the pruritus score and the body surface area affected. These data demonstrate the consistent therapeutic benefit of targeting the IL-4/IL-13 axis with dupilumab for individuals with moderate to severe AD. Additional clinical trials are currently evaluating the therapeutic benefit of targeting IL-13 alone in AD, using the monoclonal antibodies tralokinumab and lebrikizumab (Table 1).

IL-5 is a Th2 cytokine that plays a critical role in eosinophil differentiation, activation, and proliferation [61, 62]. Eosinophils play a significant role in allergic inflammation and have previously been shown to be elevated in both the circulation and lesional skin of patients with AD [63]. Similarly, levels of IL-5 are significantly elevated in the lesional skin of patients with AD and the levels in the circulation correlate with increased serum IgE [42]. Us-
ing a murine model of allergic inflammation, knocking out IL-5 resulted in reduced numbers of infiltrating eosinophils and epidermal thickening following exposure to allergens [64], suggesting a potential application for IL-5 blockade in patients with AD (Table 1). Interestingly, the administration of mepolizumab, a fully humanized monoclonal antibody targeting IL-5, did not significantly reduce skin disease severity or pruritus in patients with AD, despite reducing the eosinophils in the circulation by approximately 60% [65]. Investigators further demonstrated that treatment with mepolizumab failed to significantly reduce the size of the reactions and the tissue eosinophils in patients with AD during the atopy patch test [66]. These results suggest that a reduction of circulating eosinophils is insufficient to significantly modulate AD disease severity. Additional therapies targeting the IL-5 axis (i.e. reslizumab and benralizumab) are currently under investigation for the treatment of eosinophilic asthma, and could be evaluated for their ability to prevent the migration of eosinophils into the skin and the subsequent disease improvement. This has potential to be tailored towards personalized medicine for patients with moderate to severe AD and elevated baseline eosinophils.

### Targeting the Th2-Associated Epithelial Cytokine Thymic Stromal Lymphopoietin

Thymic stromal lymphopoietin (TSLP) was initially identified in a mouse thymic stromal cell line and is largely produced by epithelial cells in response to microbial invasion or tissue injury [67]. TSLP and TSLP receptor (TSLPR) are elevated in the lesional skin of patients with AD [68, 69] and mediate signaling through dendritic cells

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**Table 1. Intervventional studies in AD targeting the Th2 axis**

<table>
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<tr>
<th>Immunologic target</th>
<th>Agent</th>
<th>Manufacturer</th>
<th>Registered clinical trials</th>
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Targeting the Th2 Axis in AD

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Omalizumab, a humanized IgG1 monoclonal antibody against IgE, was first developed for patients with severe asthma. Given the overlapping atopic nature with asthma and increased IgE levels, omalizumab was also evaluated in patients with AD who were not adequately controlled with standard therapy. Several studies have evaluated omalizumab in adult and pediatric patients controlled with standard therapy. Several studies have demonstrated that omalizumab significantly reduces skin symptoms and marks of AD in adult and pediatric patients with moderate to severe AD [87, 88].

**Chemoattractant Receptor-Homologous Molecule Expressed on Th2 Cells**

Approximately 80% of patients with AD are sensitized to allergens, as demonstrated by increased allergen-specific IgE [24]. Subsequent exposure to these allergens triggers mast cell activation and the release of prostaglandin D2 (PGD₂), which drives inflammation by engaging with its 2 G protein-coupled receptors, D prostaglandin receptor (DP), and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) [77]. Engagement of PGD₂ with CRTH2 has been implicated in the pathogenesis of allergic diseases, including AD, by mediating the recruitment and activation of Th2 cells, innate lymphoid cells, eosinophils, and basophils [77]. Using a murine model of AD through ovalbumin sensitization, DP2 agonists were shown to increase eosinophil recruitment and skin inflammation through CRTH2 [78]. Additional murine studies have shown that pharmacological blockade of CRTH2 signaling can significantly reduce allergic inflammation in models of antigen-induced inflammation and AD [79–83]. Specifically, a CRTH2 antagonist inhibited 52% of ear swelling in fluorescein isothiocyanate-induced hypersensitivity in mice (a model of AD) and showed good pharmacokinetic parameters in mice and rats [82, 83]. Additionally, CRTH2 expression is increased in AD patients [84] and increased numbers of circulating T cells expressing CRTH2 have been shown to correlate with the severity of AD [85]. Several CRTH2 antagonists are currently under investigation for moderate to severe AD including QAW039 (Fevipiprant; Novartis) and OC000459 (Atopix), but the results have not been published (Table 1).

**Immunoglobulin E**

As elevated levels of serum IgE and allergen sensitization are found in approximately 80% of patients with AD [86], an allergic IgE-mediated disease pathogenesis has been historically hypothesized, by which high levels of the Th2 cytokines IL-4 and IL-13 in AD skin lesions could influence Ig class-switching, promoting IgE production [87, 88]. Omalizumab, a humanized IgG1 monoclonal antibody against IgE, was first developed for patients with severe asthma. Given the overlapping atopic nature with asthma and increased IgE levels, omalizumab was also evaluated in patients with AD who were not adequately controlled with standard therapy. Several studies have evaluated omalizumab in adult and pediatric patients controlled with standard therapy. Several studies have evaluated omalizumab in adult and pediatric patients...
with AD; however, the treatment effect is inconsistent and has not provided a clear clinical benefit in all patients [89–94]. A single-center, randomized, placebo-controlled, double-blind investigation (NCT01179529) was conducted with omalizumab in 20 adult patients with severe AD. Treatment with omalizumab reduced IgE levels, as expected, and had the added benefit of reducing pruritus. Despite these modulatory effects, omalizumab treatment did not significantly reduce skin disease severity [95]. Recently, an investigator-initiated study demonstrated that patients with severe AD with mutations in the FLG gene did not benefit from treatment with omalizumab, while those who lacked these mutations presented with an improvement in their skin disease severity [96]. This further illustrates the heterogeneity within AD and the potential role of biomarkers in identifying subpopulations of AD patients who could benefit from anti-IgE therapy.

Ligelizumab is a human monoclonal antibody that targets IgE with a higher affinity than omalizumab. Initial studies with ligelizumab treatment demonstrated a superior pharmacodynamic effect of IgE suppression in atop-ic patients, compared with omalizumab [97]. Based on these encouraging results, ligelizumab was further evaluated in more targeted atopic diseases including AD and allergic asthma. A randomized, double-blind, placebo-controlled trial was conducted in patients with moderate to severe AD (NCT01552629); however, subcutaneous administration of 280 mg of ligelizumab every 2 weeks for 12 weeks did not significantly decrease the severity of AD, as assessed by EASI50 response at week 12, compared with placebo [98]. One hypothesis for the overall lack of a significant therapeutic effect with IgE antagonism is that IgE synthesis and production are downstream of the cellular signaling pathways associated with AD pathogenesis, thereby limiting the effectiveness of IgE neutralization in patients with recalcitrant disease.

**Conclusion**

AD is a chronic skin disease with a high prevalence in both children and adults, and, in many cases, it constitutes the initial step in the development of other potentially severe atopic disorders. Specifically, AD is associated with a substantial patient burden that typically includes poor quality of life, sleep disturbances, and a reduction in school or work productivity [99]. Patients with AD were found to have lower physical vitality, social functioning, and emotional and mental health scores, compared with a psoriasis cohort [100]. Given the significant impact of AD on the overall quality of life of patients, there is a clear need for novel therapies that are safe and effective in the management of moderate to severe AD.

Two competing hypotheses have been suggested to describe the onset and pathogenesis of AD. The outside-in hypothesis proposes that the impaired skin barrier results from a genetic defect in epithelial cells and leads to increased allergic sensitization and AD. Many treatments for AD have focused on restoring the protective skin barrier to reduce the epidermal inflammation associated with the disease. These topical treatments provide transient disease resolution in patients with the milder forms, but they do not provide long-term relief for those with severe, recalcitrant disease. Additionally, these therapies fail to systemically modulate the pathways integral to disease initiation and pathogenesis [33].

The inside-out hypothesis suggests that AD is a systemic disease that results from an immunological abnormality, predisposing individuals to IgE-mediated sensitization. Emerging therapies provide the opportunity to systemically modulate these inflammatory pathways associated with disease pathogenesis. The varied effectiveness of treatments targeting different inflammatory pathways highlights the heterogeneity and complexity of AD and the need for focused therapy for this disease. As new therapies emerge for the treatment of individuals suffering from this debilitating disease, it will be important to further characterize the heterogeneity of patients in an effort to delineate the populations that will benefit from targeted therapy. Specifically, it is widely agreed that the central event in the pathogenesis of AD is the activation of the Th2 cytokine axis that results in an increased inflammatory response, disruption of the skin barrier, increased susceptibility to infections, and increased allergen sensitization. Novel therapies, such as those described here, that target the Th2 signaling axis, have the potential to revolutionize the management of AD by introducing less harmful and more effective treatment strategies.

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