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ALLERGIC SKIN DISEASES (LUZ FONACIER AND ANDREAS WOLLENBERG, SECTION EDITORS)

New and Potential Treatments for Atopic Dermatitis: Biologicals and Small Molecules

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Abstract

Purpose of Review An update on new therapies currently approved or potentially useful in the future for the management of patients suffering moderate-to-severe atopic dermatitis.

Recent Findings New pathogenic mechanisms involved in atopic dermatitis have permitted to propose novel therapeutic approaches devised to control the inflammatory process observed in involved cutaneous tissues by neutralizing mediators, cytokines, and their receptors.

Summary Recent research findings have disclosed important and previously unrecognized pathogenic mechanisms that have resulted in innovative targeted therapies, such as dupilumab, and potentially other biologicals and small molecules. Further studies should permit the sub-classification of patients according to the relevance of different mediators and inflammatory cells. It can be concluded that the treatment of atopic dermatitis has entered into the era of personalized/precision medicine.

Keywords Atopic dermatitis · Biologicals · Dupilumab · Eczema · Small molecules · Treatment

Abbreviations

IGA	Investigator Global Assessment
EASI	Eczema Area and Severity Index
TSLP	Thymus stromal lymphopoietin
ILC	Innate lymphoid cell
SCORAD	Scoring of Atopic Dermatitis

This article is part of the Topical Collection on *Allergic Skin Diseases*

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Introduction

Atopic dermatitis (AD) is a chronic recurrent inflammatory disease of the skin characterized by pruritus and eczema with typical anatomic localization according to age. It affects 15–30% of children and 2–10% of adults [1–3]. In the group 6–7 years old, prevalence rates vary between 0.9% (India) and 22.5% (Ecuador), and in 13–14-year-old adolescents, these range between 0.2% (China) and 24.6% (Colombia) [4].

The diagnosis of AD is based on the presence of pruritus, eczema, typical morphology, and a chronic or recurrent history (Figs. 1 and 2). Other important features include early life symptoms, atopy, increased total and specific IgE, and xerosis. Associated features frequently present are atypical vascular responses, keratosis pilaris, pityriasis alba, hyperlinear palms, ocular ichthyosis, periorbital and perioral dermatitis (Fig. 3), perifollicular accentuation, lichenification (Fig. 4), and prurigo [5•].

The following clinical phenotypes of AD, according to age of onset, have been recently proposed by Bieber et al.: (1) very early onset with remission, (2) early onset,

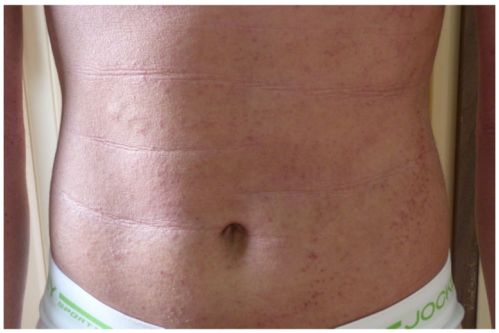

Fig. 1 Extensive eczematous lesions on abdominal skin of an 18-year-old male patient with atopic dermatitis

(3) childhood onset, (4) adolescent onset, (5) adult onset, (6) very late onset [6••].

In addition to the adverse effects of AD on mental health and quality of life, recently associations of AD with various comorbidities, including systemic nonallergic conditions such as obesity, cardiovascular disease, autoimmunity, and malignancies, have been highlighted (Fig. 5) [7].

In this article, the pathogenic basis of AD is briefly reviewed in order to discuss novel and potential therapeutic approaches based in recently acquired knowledge and clinical trials that have led to the incorporation of new biologicals and anti-inflammatory medications for the control of the disease.

Pathogenesis of Atopic Dermatitis

Genetic and environmental factors contribute to the cutaneous inflammatory process. Up to 70% of patients have a family history of atopic diseases [8]. Immunological mechanisms involve an immune deviation towards Th2/Th22 pathway leading to increased IgE production with later activation of Th1 and Th17 pathways [9•].

Additionally, a deficient skin barrier function associated to genetic polymorphisms of filaggrin and other genes, microbial skin colonization with *Staphylococcus aureus* or *Malassezia furfur*, and increased susceptibility to skin infections have been reported (Fig. 6) [10–13].

In adults with AD, Th2 and Th22 cells are increased in the blood, whereas in children, the peripheral blood phenotype is characterized only by Th2 expansion, with increased innate and Th17-related inflammation in early AD lesions of infants and increased levels of antimicrobial peptides [14].

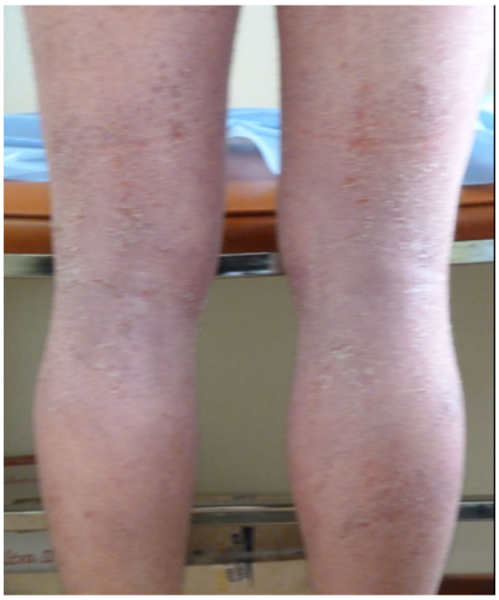

Fig. 2 Flexural and lower limb eczema with erythema and desquamation in a 21-year-old patient with atopic dermatitis. Total serum IgE 1247.4 kU/L.

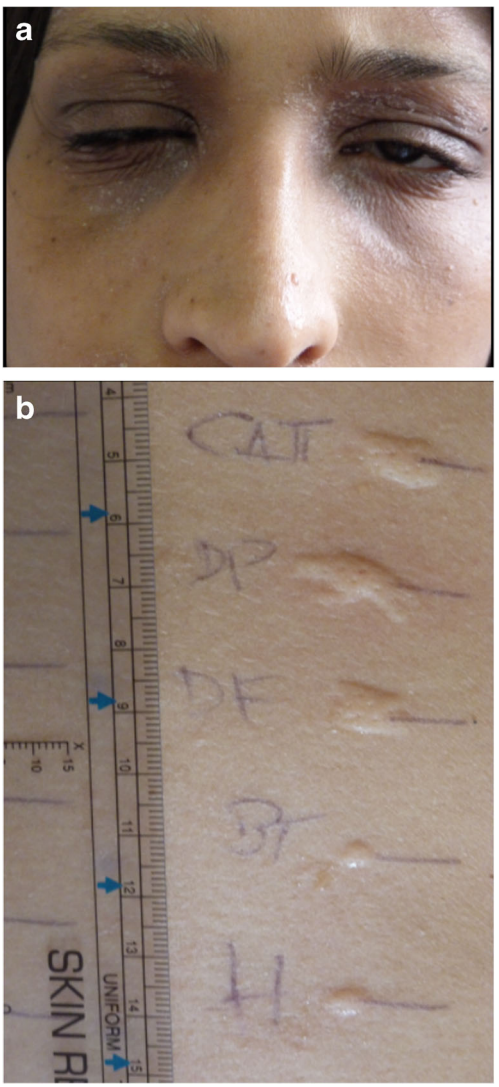

Fig. 3 **a** Eyelid dermatitis in a 24-year-old female atopic patient. She had extensive lesions on trunk, upper and lower limbs, peripheral blood eosinophilia 16%, and total serum IgE 350 kU/L. **b** Prick tests to allergen extracts were positive to cat, *Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farinae* (DF), and *Blomia tropicalis* (BT). H histamine positive control

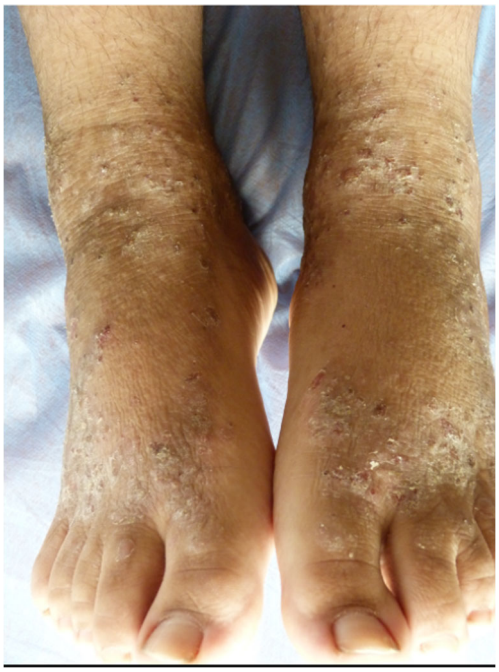

Fig. 4 Severe chronic lesions on the feet of an 18-year-old atopic patient with clinical picture of rhinitis and dermatitis. Skin lesions were also present on flexural surfaces of elbows and knees, arms, forearms, and wrists

Management of Atopic Dermatitis

General measures that are currently recommended for the treatment of AD are summarized in Table 1. Those include the regular use of emollients and humectants to treat the skin dryness and repairing the skin barrier, regular bathing, topical anti-inflammatory therapy with corticosteroids and calcineurin inhibitors (tacrolimus, pimecrolimus), topical crisaborole, and topical antimicrobials to eradicate bacterial (*Staphylococcus*) colonization. Occasionally systemic antibiotics, diluted bleach baths, and antiviral therapy are required for secondary skin infections.

In patients with severe disease or those non-responding to the above mentioned measures, phototherapy and systemic immune modulators (cyclosporine, methotrexate, mofetil mycophenolate, azathioprine) have been employed [15•].

Similar to other chronic diseases, patient education encompassing general knowledge on the chronic nature of the disease and the importance of protective and general care of the skin has primordial importance. Adherence to the treatment and correct techniques for the application of topical therapies are to be reinforced.

New therapies for the treatment of AD have been recently incorporated, including new biologicals (Table 2) and small molecules (Table 3) designed to interfere with the pathogenic mechanisms of the disease. These will be discussed in the following sections.

Biologicals for the Treatment of Atopic Dermatitis

Since a high proportion of patients suffering severe AD do not exhibit satisfactory responses to conventional therapies, new modalities of treatment are being investigated. These include biological agents with immunomodulatory and anti-inflammatory properties, including monoclonal antibodies and small molecules.

Some biologicals that have shown limited efficacy in AD patients are monoclonal anti-IgE (omalizumab), anti-TNF (infliximab), anti-recruiting/activation of T cells (efalizumab, alefacept), anti-IL-4/13 (pitrakinra), anti-IL-5 (mepolizumab), and anti-CD20 (rituximab) [16]. The only monoclonal antibody currently approved by

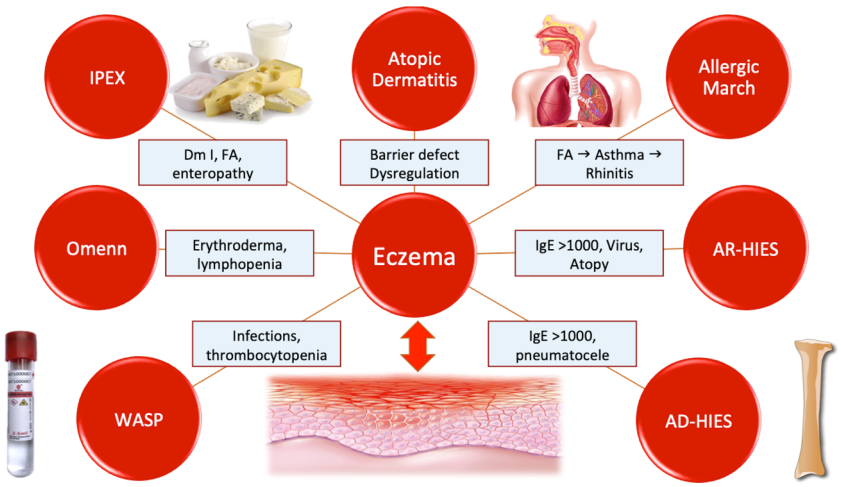

Fig. 5 Comorbidities and differential diagnosis of atopic dermatitis

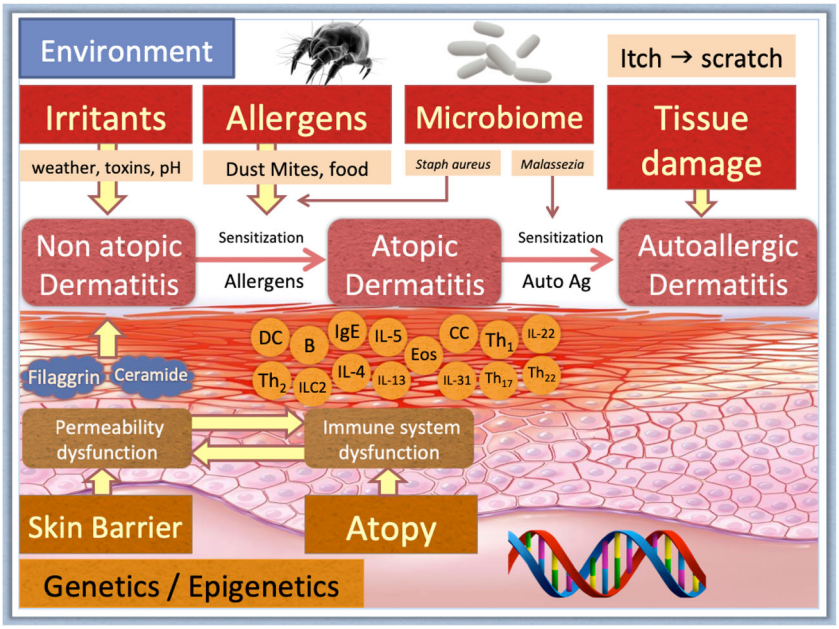

Fig. 6 Pathogenesis of atopic dermatitis

European and US regulatory authorities for the treatment of AD is anti-IL-4Rα (dupilumab) [17•]. However, a number of additional monoclonal antibodies that interfere with various inflammatory pathways involved in the pathogenesis of AD are promising and are actively being investigated, such as anti-thymus stromal lymphopoietin (TSLP) (tezepelumab), anti-IL-31RA (nemolizumab), anti-IL-13 (tralokinumab and lebrikizumab), anti-OX40R (GRB830), anti-IL-17A (secukinumab), anti-IL-22 (fezakinumab), anti-IL-12/IL-23p40 (ustekinumab), anti-IL-19, and anti-IL-33 (Table 2) [14, 18, 19].

Efficacy and Safety of Dupilumab in Patients with Atopic Dermatitis

IL-4 and IL-13 induce cellular activation through binding to a common alpha chain present in both, IL-4 and IL-13 receptors. Dupilumab is a monoclonal antibody that interferes IL-4 and IL-13 functions by binding this alpha chain [17•]. Thus, dupilumab blocks multiple inflammatory pathways that include Th2 cell activation and the production of a number of cytokines and chemokines [14].

The clinical efficacy and safety of dupilumab in AD has been investigated in various double-blind placebo-controlled studies that observed significant improvements in the Eczema Activity Severity Index (EASI-50 and EASI-75), the Investigator Global Assessments (IGAs), and reduction of pruritus, as well as other secondary endpoints [14, 20•, 21•, 22]. These results led to the approval of dupilumab indication for patients with moderate-to-severe AD by the FDA of the USA in 2017. In those studies, the only remarkable adverse effect consisted in an increased rate of conjunctivitis in the group of patients receiving dupilumab as compared with those treated with placebo [20•].

Other Biologicals Under Investigation

A number of additional biological agents that are being tested in patients with AD are directed to block the actions of different cytokines or their receptors, such as IL-5, IL-12/IL-23, IL-13, IL-17A, IL-22, IL-31, IL-33, TSLP, and Ora 1 [18, 19].

Table 1 Management strategies for patients with atopic dermatitis

1. Emollients/humectants
2. Topical corticosteroids
3. Topical immunomodulators: calcineurin inhibitors, crisaborole
4. Topical antimicrobials and antiseptics
5. Immune modulators
6. Phototherapy
7. Biologicals
8. Small molecules

Table 2 Biological medications for atopic dermatitis

Biological	Development status
Dupilumab	Approved by FDA for moderate-to-severe AD
Anti-TSLP (tezepelumab)	Phase 2
Anti-IL-12/IL-2p40 (ustekinumab)	Phase 2
Anti-IL-13 (tralokinumab, lebrikizumab)	Phase 3
Anti-IL-17A (secukinumab)	Phase 2
Anti-IL-19	NA
Anti-IL-22 (fezakinumab)	Phase 2
Anti-IL-31 (BMS981164)	Phase 1
Anti-IL-31RA (nemolizumab)	Phase 2
Anti-IL-33	NA
Anti-OX40R (GRB830)	NA

NA not available

Anti-IL-12/23

In AD lesions, mRNA expressions of the p40 cytokines IL-12 and IL-23 are similarly upregulated at an even higher level than in psoriasis tissues. Interestingly, p40 and IL-23R have also been found to be significantly upregulated in non-lesional AD skin [23].

Ustekinumab is a mAb that blocks the cytokines IL-12 and IL-23 by targeting the common p40 subunit shared by these cytokines, thereby inhibiting Th1 and Th17/Th22 responses, respectively [24]. A double-blinded, placebo-controlled, crossover designed, phase II study to investigate the safety and efficacy of ustekinumab in 33 patients with moderate-to-severe AD over a 40-week period has been recently published. Background therapy with the low-potency (class VI) topical steroid triamcinolone acetonide (0.025%) cream was provided throughout the study. The ustekinumab group achieved higher Scoring of Atopic Dermatitis (SCORAD) 50 responses at 12 weeks, 16 weeks (the primary endpoint), and 20 weeks compared to placebo, but the difference between groups was not significant. The AD molecular profile/transcriptome showed early robust gene modulation, with sustained further improvements until 32 weeks in the initial ustekinumab group. Distinct and more robust modulation of Th1, Th17, and Th22 as well as Th2-related AD genes (i.e., MMP12, IL-22, IL-13, IFN-γ, elafin/PI3, CXCL1, CCL17; $p < 0.05$) was seen after 4 weeks of ustekinumab treatment. Epidermal responses (K16, terminal differentiation) showed faster (4 weeks) and long-term regulation (32 weeks) from baseline in the ustekinumab group. No severe adverse events were observed. Ustekinumab had clear clinical and molecular effects, but clinical outcomes might have been obscured by a profound "placebo" effect, most likely due to background topical glucocorticosteroids and possibly insufficient dosing for AD [25].

Table 3 Small molecules under investigation for the treatment of atopic dermatitis

Target	Medication	Investigational phase
CRTH2	OC000459	2a → Stop
CRTH2	QAW 039	2b → Stop
PDE4	Apremilast	2a → Stop
PDE4	Crisaborole	Approved for mild-moderate AD
H4R	ZPL 389	2a*
JAK 1/2	Baricitinib	2b*
JAK 1	Pf-04965842	2a*
JAK 1	Upadacitinib (ABT494)	2a*
NK1R	VLY-686/tradipitant	2a*
NK1R	Serlopitant	2a*

*Ongoing

Stop drug development program stopped

Anti-IL-13

IL-13 is overexpressed in skin biopsies from patients with AD and levels of IL-13 mRNA correlate with disease severity [26, 27].

Lebrikizumab, a monoclonal antibody that specifically binds with high affinity to soluble IL-13, was superior to placebo in patients with AD when administered subcutaneously every 4 weeks along with topical corticosteroids. Authors suggested that IL-13 inhibition could reduce the need for oral immunosuppressive therapy in those patients. In a randomized, placebo-controlled, double-blind, phase 2 study, adults with moderate-to-severe AD with an inadequate response to

topical corticosteroids received lebrikizumab 125 mg single dose, 250 mg single dose, 125 mg every 4 weeks for 12 weeks, or placebo. After week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg every 4 weeks (82.4%, $p = 0.026$) than placebo (62.3%). Adverse events were similar between groups (lebrikizumab 66.7%, placebo 66.0%). [28].

Another phase 2b study investigated the effects of tralokinumab, a fully human IgG4 monoclonal antibody that neutralizes potently and specifically IL-13, in adults with moderate-to-severe AD who received 45, 150, or 300 mg of tralokinumab or placebo every 2 weeks for 12 weeks through the subcutaneous route with concomitant topical glucocorticoids. At week 12, 300 mg of tralokinumab significantly improved the change from baseline EASI score versus placebo (−4.94; 95% CI −8.76 to −1.13; $p = 0.01$), and a greater percentage achieved an Investigator Global Assessment (IGA) response (IGA of 0 or 1 and a reduction of 2 grades or more from baseline to week 12) (26.7% vs 11.8%). Also, in patients receiving 300 mg of tralokinumab, improvements in SCORAD, quality of life (DLQI), and pruritus scores were observed [29]. Increased responses to tralokinumab were present in patients with higher DPP-4 and periostin, two biomarkers of IL-13 activity [30]. Upper respiratory tract infections and headache were the most common adverse effects.

Anti-IL-17

Production of Th17 cells is stimulated by TGF-β, IL-6, IL-1β, IL-7, IL-21, and IL-23, whereas it is inhibited by IL-27, IFN-γ, IL-4, and IL-5. Th17 lymphocytes produce IL-17, whereas type 3 innate lymphoid cells (ILC3) cells produce the Th17 cytokines IL-17 and IL-22. The IL-17 family of cytokines is a group of homologous proteins constituted by IL-17A and IL-17B to IL-17F. The synthesis of IL-17 is strongly stimulated in AD. IL-17C derived from epithelial cells/keratinocytes is involved in inflammation in both psoriasis and AD, being also induced by bacteria through TLR2 and TLR5. IL-17C acts through IL-17RA and IL-17RE receptors localized in T lymphocytes and keratinocytes. It stimulates Th17 cells to produce IL-17A/F and IL-22. In mice with AD, Th2 response is regulated by IL-17, and the lack of IL-17A reduces dermatitis and IL-4 and IgE production [31]. Additionally, IL-17 induces the production of cytokines such as IL-8, TNF-α, and TSLP, the chemokines CCL17 and CXCL10, and antimicrobial peptides that regulate Th2 responses and lead to chronic AD. It also inhibits filaggrin expression. In peripheral blood of patients with AD, the number of Th17 cells is elevated, especially in acute lesions [32].

Secukinumab is a monoclonal antibody directed against IL-17A. It has been suggested that the subset of AD patients characterized by low IgE levels and increased activation of Th17 can respond to anti-IL-17 therapy [33].

The monoclonal antibody against IL-17C MOR106p was evaluated in a randomized, double-blind, placebo-controlled phase 1 trial in 25 patients with AD, and it was found that EASI-50 was achieved in 83% of patients at week 4, and the effects lasted for over 2 months [34].

Anti-IL-31

Pruritus of AD is mediated by histamine-dependent and histamine-independent mechanisms. IL-31 secreted by T cells induces pruritus [9•]. Subcutaneous nemolizumab, an anti-IL-31 monoclonal antibody, has been shown to reduce pruritus in patients with AD [35, 36]. Improvement from baseline in dermatitis scores was also maintained/increased to week 64 (percentage change in the Eczema Area and Severity Index scores 268.5, 275.8, 278.9, and 269.3 in the 0.1-, 0.5-, and 2.0-mg/kg Q4W and 2.0-mg/kg Q8W groups, respectively) [36].

Anti-IL-33

IL-33 is an alarmin that belongs to IL-1 superfamily and is secreted by macrophages, dendritic cells, fibroblasts, adipocytes, smooth muscle cells, endothelial cells, bronchial epithelium, osteoblasts, and intestinal epithelial cells and myofibroblasts after cell damage signals. IL-33 binds to a specific toll receptor (TLR)/IL-1R superfamily, the suppression of tumorigenicity (ST2) receptor, which forms a heterodimer with the IL-1R-associated protein (IL-1RAcP), initiating the immune cascade [37]. IL-33R ST2 is a member of toll-like receptor/IL-1R superfamily highly expressed in macrophages, eosinophils, dendritic cells, mast cells, basophils, NK cells, ILC2 cells, Th2 lymphocytes, and B cells, as well as the endothelium, epithelium cells, and fibroblasts.

IL-33 binding to ST2 or IL-1RAcP receptors engages MyD88 and a number of kinases: (IRAK)1/4, IRAK1/2, p38 MAPK, (TNF)R-associated factor 6 (TRAF 6), and JNK. It stimulates NF-κB transcription and the production of Th2-dependent cytokines. Additionally, IL-33 activates mast cells and basophils and causes its migration, maturation, adhesion, and survival.

There is overexpression of IL-33 in the epidermis and infiltration of ST2-positive cells in patients with AD. IL-33 also stimulates ILC2 cells [38, 39]. Patients with AD have significantly elevated serum levels of IL-33 [40, 41].

Other observations indicate that IL-33 and ILC2 cells play important roles in the skin barrier dysfunction. Most patients

with AD display a reduced expression of filaggrin, involucrin, and loricrin. IL-33 downregulates filaggrin expression in keratinocytes [39].

In mice anti-IL33 antibody treatment results in the improvement of AD whereas IL-33- or ST2-deficient mice show diminished AD symptoms [42, 43]. These observations indicate a potential role for anti-IL-33 therapy in patients with AD.

Anti-Thymic Stromal Lymphopoietin (Anti-TSLP)

It has been demonstrated that the concentration of TSLP in the serum from children and adults with AD is increased [44], and higher TSLP expression has been observed in keratinocytes from AD patients [45], which correlated with disease severity [46]. Carriers of the genotype CC of the TSLP gene, rs2289278, showed an increased risk of developing AD [47].

Tezepelumab, an antibody directed against circulating TSLP, has been investigated in a phase IIa randomized, double-blind, placebo-controlled study in which 113 patients were randomized 1:1 to subcutaneous tezepelumab 280 mg or placebo every 2 weeks, plus class 3 topical corticosteroids (TCS). The primary endpoint was the week 12 response rate for a ≥ 50% reduction in the Eczema Area and Severity Index (EASI50). Secondary endpoints including EASI75, Investigator's Global Assessment, Scoring of Atopic Dermatitis (SCORAD) 50, SCORAD75, pruritus numeric rating and 5-D itch scales, and exploratory endpoints (including EASI90) were assessed at week 12 and week 16 (post hoc). A numerically greater percentage of tezepelumab plus TCS-treated patients achieved EASI50 (64.7%) versus placebo plus TCS (48.2%; $p = 0.091$). Numerical improvements over placebo were demonstrated for week 12 secondary and exploratory endpoints, with further improvements at week 16. Treatment-emergent adverse events were similar between treatment groups. Authors concluded that, although not statistically significant, numerical improvements over placebo for all week 12 endpoints were demonstrated, with greater week 16 responses [48].

IL-19 and Atopic Dermatitis

IL-19 is a pro-inflammatory cytokine that stimulates the production of Th2 cells. Under the influence of IL-17A, IL-19 is strongly expressed in AD lesional skin. There are no published studies dealing with inhibition of IL-19 in atopic dermatitis.

Small Molecules

The therapeutic usefulness of a number of small molecules in AD is currently being investigated. The following molecules are in phase 2 studies that involve patients with moderate-severe AD: anti-H4R (ZPL 389), anti-JAK ½ (baricitinib), anti-JAK 1 (Pf-04965842, upadacitinib, ABT 494), anti-NK1R (VLY-686/tradipitant), anti-NK1R (serlopitant) [14, 18] (Table 3).

Topical crisaborole was recently approved by US regulatory authorities for the treatment of mild-to-moderate AD. This is a boron compound that inhibits PDE-4, the enzyme that converts cAMP to AMP. In consequence, accumulation of increased levels of cAMP inhibits the activation of NF-κB and the production of inflammatory mediators. When compared with vehicle control, crisaborole induced significant improvement in IGA score and pruritus. It is well tolerated in intertriginous and facial skin, and the most common adverse effect is application site pain/burning at mild-to-moderate intensity [49].

Conclusions

Atopic dermatitis is a major health problem in patients of all ages and compromises severely the quality of life of a significant number of affected individuals. Recent research findings have disclosed important and previously unrecognized pathogenic mechanisms that have resulted in innovative targeted therapies such as dupilumab and potentially other biologicals and small molecules. Further studies should permit the subclassification of patients according to the relevance of different mediators and inflammatory cells. It can be concluded that the treatment of atopic dermatitis has entered into the era of personalized/precision medicine.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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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- • Of importance
- •• Of major importance

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