

Immunologic Targets in Atopic Dermatitis and Emerging Therapies: An Update

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Abstract Atopic dermatitis is one of the most common chronic inflammatory skin diseases. It usually begins in childhood, has a considerable impact on patients' quality of life, and incurs substantial healthcare costs. The standard-of-care treatments for patients with moderate to severe disease are very limited and have variable and typically insufficient efficacy and many side effects, some of which are quite serious. However, over the last decade, considerable advances in our understanding of the pathogenesis of atopic dermatitis have paved the way for a number of new treatments. Most notable are the drugs that target the Th2-polarized immune system, which is thought to play a key role in many of the signs and symptoms characteristic of this disease. In this article, we briefly review the pathophysiology of atopic dermatitis, while noting that each patient's disease phenotype is likely due to a unique interplay of several disease-specific dysregulated pathways. Lastly, we cover emerging therapies for atopic dermatitis, focusing on those that target specific components of the immune system, which are altered in atopic dermatitis. The hope is that these new biologics or small-molecule antagonists, which have high specificity for their target molecules, will decrease the undesirable side effects caused by off-target effects commonly observed with current immunosuppressive agents that are characterized by broad biological actions.

Key Points

We now have a greater understanding of the role that Th2 cytokines play in the pathogenesis of atopic dermatitis.

Multiple drugs targeting specific components of the Type 2 immune response are in development as systemic treatments for atopic dermatitis.

It is hoped that these and other targeted therapies will improve the immune dysregulation and skin barrier dysfunction observed in most subjects with atopic dermatitis and have fewer off-target effects.

1 Introduction

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases. It is characterized by immune dysregulation, skin barrier defects, increased susceptibility to skin infections, intense pruritus, and epidermal hyperplasia [1–3]. The prevalence of AD is high, with rates as high as 25 % in children and 10 % in adults, and is most prevalent in climates characterized by low humidity, ultraviolet (UV) indices, and temperatures [4]. The disease has a substantial impact on quality of life of the affected individuals and their families and is associated with substantial healthcare costs, similar to those of emphysema, psoriasis, and epilepsy [5, 6]. These effects become more pronounced as disease severity increases, especially since therapeutic options are very limited in patients with moderate to severe disease. Commonly used therapies include topical emollients, topical anti-inflammatory agents

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(corticosteroids and calcineurin inhibitors), and sedating antihistamines. These agents can individually and collectively provide significant relief for those with mild disease [7]; however, they are frequently inadequate for patients with moderate to severe disease, and studies have shown that most providers resort to intermittent courses of systemic steroids and, less commonly, phototherapy to manage this group. A remarkably small percentage of physicians utilize a host of systemic immunosuppressants, all of which are off label, as steroid-sparing agents in this more recalcitrant group [8, 9]. Of the more commonly used systemic immunosuppressants, cyclosporine has the strongest evidence for efficacy in AD, but its long-term use is limited because of the relatively common side effects of hypertension and nephrotoxicity as well as a host of other less frequent complications, not the least of which is the increased risk of infections and malignancy [10]. Cyclosporine is approved for the treatment of AD in Japan and several European countries but not in the USA or Canada. Other immunosuppressants used to treat AD include azathioprine and methotrexate, but these come with their own unique side effects [10]. There is limited evidence to support the use of gamma interferon, systemic tacrolimus, rapamycin, rituximab, omalizumab, and intravenous immunoglobulins (IVIG) in the treatment of AD [10]. Data about the benefits of allergen-specific immunotherapy as an adjunctive AD treatment are conflicting [11]. The confusion surrounding AD pathogenesis may be partly responsible for the paucity of effective and safe systemic treatments, but significant progress has been made in our understanding of this common skin condition over the last decade. This advancement has led to the development of targeted treatments that will hopefully be not only effective but also will have reduced side effects compared with currently available therapies that have broad actions and consequently side effects due to off-target actions. We provide an overview of our current understanding of AD pathogenesis and in that context also provide an update on new therapies being developed. There is little doubt we are entering an exciting new era that will likely revolutionize our ability to modulate this common, chronic, and debilitating skin disease.

2 Atopic Dermatitis (AD) Pathogenesis

Two seemingly competing theories have been proposed to explain the development of AD: the so-called outside-in and inside-out hypotheses. The premise in the outside-in hypothesis is that a primary skin barrier defect leads to AD. This idea posits that a compromised epidermal barrier results in enhanced trans-epidermal water loss (TEWL), which likely explains the xerosis or dryness observed in

most patients, as well as greater penetration of allergens and irritants and possibly also increased risk of skin colonization and infections [12]. Some literature suggests that barrier disruption may promote an ‘allergic’ or Type 2 immune response characterized by the production of the cytokines interleukin (IL)-4 and IL-13 [13–15]. Epithelial cells by virtue of their expression of pattern recognition receptors (PRRs) also recognize a number of allergens and play an important immunomodulatory role in addition to their barrier attributes [16]. The inflammatory cascade that occurs in response to allergen exposure leads to dendritic cell (DC) maturation and differentiation and ultimately to type 2 T-helper lymphocyte (Th2)-mediated inflammation [17]. This has led some to suggest that the skin may be the primary organ for allergen sensitization in all atopic diseases and might explain the relatively high rates of other atopic diseases in subjects with AD (e.g. >30 % with asthma, >60 % with allergic rhinitis, and >30 % food allergy [in children aged ≤5 years with moderate to severe AD]) [17, 18]. This outside-in or barrier hypothesis was more widely embraced after the identification of null mutations in the stratum corneum protein called filaggrin (*FLG*), which strongly associated with AD [19, 20]. We now know that the presence of *FLG* mutations varies widely: up to 40 % of AD patients from Northern Europe carry at least one of these null mutations, other Caucasian populations have much lower allele frequencies, and individuals of African descent have very low to no *FLG* mutations [19–22]. The vast majority of individuals with an *FLG* mutation carry only one null allele, and 40 % of these subjects never develop AD; most of those who do develop AD will outgrow their disease by late childhood. In contrast, individuals with two alleles almost universally develop AD, and their disease is more persistent [23]. These observations suggest that a single *FLG* mutation is neither necessary nor sufficient to cause AD, but may simply be one of a number of critical risk factors that predict the development of AD (or its persistence). In contrast, the inside-out hypothesis argues that the primary pathology in AD is immune dysregulation or deviation that leads to activated memory Th2 lymphocytes characterized by the production of IL-4 and IL-13. Recent expression profiling studies have reaffirmed the predominance of Th2 cytokines within AD lesions but have also identified a more modest and variable expression of other T cell subsets (Th1, Th17, and Th22) [2]. Th22 cytokines are thought to induce some of the epidermal features characteristic of AD (e.g., reactive epidermal hyperplasia), whereas Th2 cytokines are thought to inhibit the expression of epidermal antimicrobial peptides (AMP), *FLG*, and other barrier proteins. Therefore, in this model, the epidermal abnormalities are secondary to the immunological features.

While the primary defect that initiates the development of AD remains elusive, AD appears to have two immunologic phenotypes, often referred to as extrinsic (or allergic) and intrinsic (or non-allergic). Eighty percent of AD patients have extrinsic disease, as defined by the presence of elevated total immunoglobulin (Ig)-E (tIgE) and specific IgE for environmental and/or food allergens. The intrinsic type has normal tIgE levels, no elevations in allergen-specific IgE, and negative skin-prick tests for common aeroallergens or food allergens [24, 25]. The outside-in or barrier hypothesis may be more important in patients with extrinsic AD, who have a higher incidence of *FLG* mutations, lower frequency of interferon (IFN)- γ producing Th1 and IL-17A-producing Th17 cells, but similar levels of Th2 cells in lesional skin (however, in blood, the frequency of Th17 cells appears similar between the intrinsic and extrinsic subtypes) [26, 27]. Ultimately, it may be impossible to determine the primary pathology in AD (immune or epithelial), as both processes may be critical for the development of the disease and their relative importance within an individual may explain some of the clinical heterogeneity observed in this disease. We now appreciate that there is a complex dance between immune and epithelial defects, with immune dysregulation leading to skin inflammation and barrier disruption, and barrier defects promoting allergen penetration and Th2 sensitization. Ultimately, we will need to understand the relative contributions of genetic and environmental (micro- and macro-) factors on these immune and barrier defects. For this review, we focus on the immune defects known to contribute to AD, as most of the emerging targeted therapies attempt to act on the immune deviations characteristic of the disease.

2.1 Innate Immune Defects

The innate immune system serves as the first line of defense against invasion by pathogens or tissue injury and acts in a fast and non-specific way, predating the adaptive immune response, which is a more specific and long-lasting defense system. Evidence suggests that dysregulation of the cutaneous innate immune system plays a critical role in the pathogenesis of AD. For the purposes of this review article, we provide a simplified overview of the innate immune system. This system utilizes PRRs, which in the context of skin biology are expressed primarily on keratinocytes and interstitial cells (DCs and mast cells), as well as host defense peptides (including AMPs). It is important to note that keratinocytes are critical cells in the skin's innate immune response by virtue of their location. They are often the sentinel cell, and many of their innate responses have downstream effects on the physical skin barrier, skin microbiome, and adaptive immunity.

The best-characterized family of PRRs is the Toll-like receptors (TLRs), which are transmembrane proteins that recognize a wide array of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). PAMPs are exogenous ligands on the surfaces of bacteria and viruses, and DAMPs are endogenous ligands released by the host in response to tissue damage. TLR2 has been particularly well studied since it recognizes several *Staphylococcus aureus* cell wall products, and patients with AD are highly susceptible to cutaneous colonization and infection with *S. aureus* [28, 29]. Reduced TLR2 expression has been demonstrated in keratinocytes and circulating monocytes from patients with AD [30]. Two *TLR2* mutations have been identified in patients with AD: the missense mutation R753Q single nucleotide polymorphism (SNP) and the A-16934 SNP found in the *TLR2* promoter, which inhibits *TLR2* transcription [31–35]. TLR2 signaling increases epidermal production of AMPs such as human β -defensins (HBD) and LL-37 (a cathelicidin), which limits bacterial growth and alters the skin microbiota [36, 37]. Signaling through TLR2 not only induces gene transcription that helps to eliminate the pathogen but is also crucial for the maintenance of tight junctions (TJs) and thus is critical in skin barrier formation and repair [38, 39]. One might postulate that this aspect of an innate immune response may help prevent persistent TLR2 activation and ensuing inflammation because TJs are present in the superficial layers of the epidermis, whereas TLR2 is expressed below these layers [28]. Interestingly, TLR stimulation can also induce keratinocyte production of thymic stromal lymphopoietin (TSLP), an important cytokine in priming the Type 2 adaptive immune response [40–42].

2.2 Adaptive Immune Defects

Adaptive immunity also plays a central role in AD pathobiology. Within AD lesions, Th2, Th22, and degranulating eosinophils predominate, with variable degrees of Th1 and Th17 [8]. The Th2 cytokines (IL-4, IL-5, and IL-13) are thought to be critical to mounting a protective immune response against infections by extracellular parasites and are critical to the pathobiology of AD and asthma (Fig. 1). Interestingly, mice develop these diseases when genetically modified to over-express these cytokines [43–49]. While IL-4 in AD is increased due to production by Th2 lymphocytes, the cell type that initially produces IL-4 to induce differentiation of naïve Th cells (Th0) into Th2 cells remains elusive. Recent research suggests that Th2 inflammation may be initiated by epithelial production of tissue alarmins such as IL-25, IL-33, and TSLP (perhaps in response to infection, tissue injury, or allergen exposure). These cytokines can act on a newly described group 2

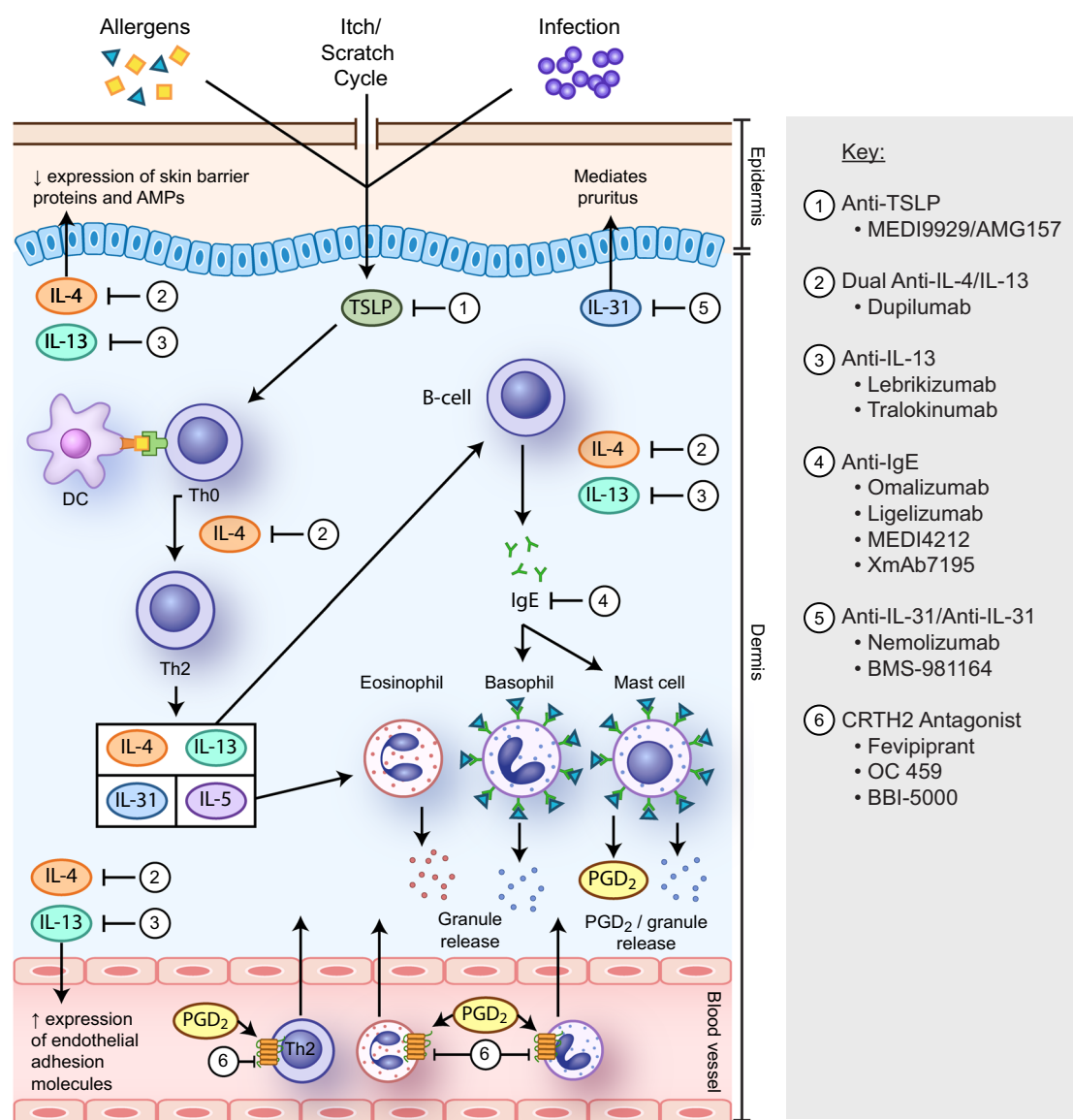


Fig. 1 Effects of therapies targeting the Type 2 immune pathways. AMP antimicrobial peptide, *CRTH2* chemoattractant receptor-homologous molecule expressed on Th2 cells, DP2, DC dendritic cell, *IgE*

immunoglobulin E, *IL*- interleukin, *PGD₂* prostaglandin D₂, *Th* T-helper, *TSLP* thymic stromal lymphopoietin

innate lymphoid cell (ILC2, also called nuocyte), present in the dermis, and this cell is a robust source of IL-5 and IL-13 [50–53]. Release of Th2 cytokines leads to even greater Th2 differentiation in a positive feedback loop. IL-4 and IL-13 signal through a shared receptor and initiate the Janus kinase (JAK) 1/3-signal transducer and activator of transcription (STAT) 6 (JAK1/3-STAT6) signaling cascade, which leads to the upregulation of the transcription factor GATA3, a master regulator of Th2 immune responses (Fig. 2) [54]. IL-4 and IL-13 promote inflammation by enhancing expression of endothelial adhesion molecules that promote the tissue migration of eosinophils, basophils, and T and B lymphocytes, and also act on B cells to

promote growth and induce isotype class switching to IgE [53, 55]. Secreted IgE binds primarily to the high-affinity IgE Fc epsilon receptors (FcεRI) on mast cells and basophils, and when crosslinked with an allergen these cells will degranulate and release their mediators [56]. IL-4 and IL-13 further drive AD by inhibiting expression of skin barrier proteins such as FLG, loricrin, and involucrin, which is thought to lead to an increased penetration of allergens and pathogens [57, 58]. In addition, they reduce the expression of innate immune response proteins, such as HBD and cathelicidins, increasing susceptibility to *S. aureus* and herpes simplex virus skin infections [59–63]. IL-5 signals through the IL-5 receptor (IL-5R), which is composed of

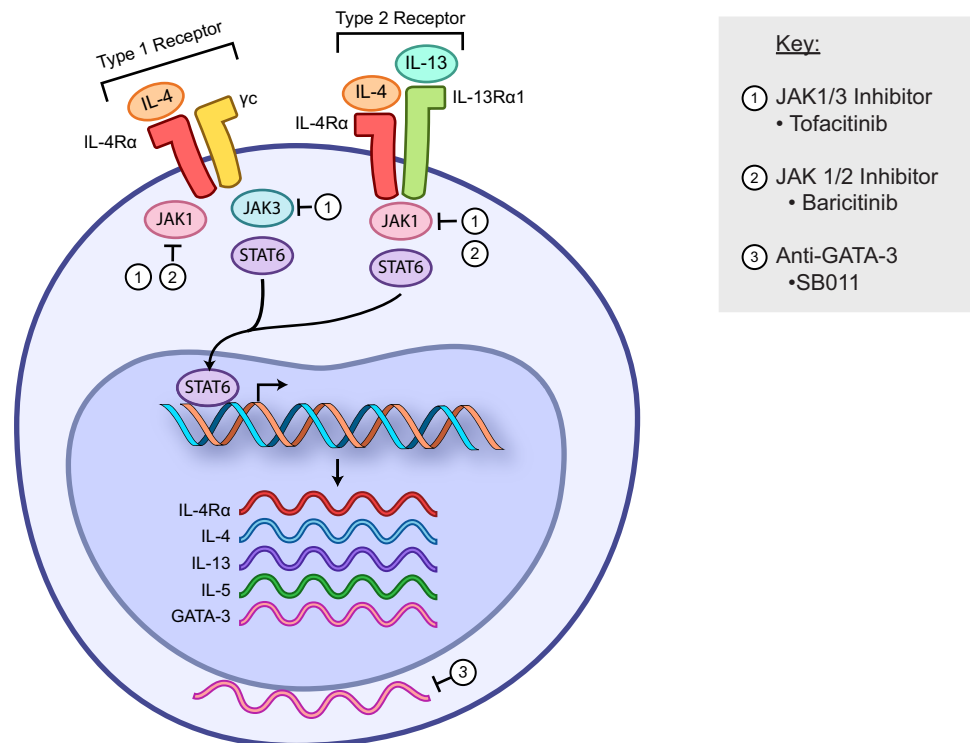


Fig. 2 Signal transduction in the Type 2 immune responses and downstream effects. -R receptor, γ c common cytokine receptor, γ -chain, GATA-3 transcription factor, master regulator of Th2 immune

responses, *IL*- interleukin, *JAK* Janus kinase, *STAT* signal transducer and activator of transcription

IL-5 α and β subunits and plays a crucial role in bone marrow production, survival, activation, and migration of eosinophils and basophils [64]. All activated Th cells, and especially Th2 cells, secrete IL-31, which is thought to play a role in pruritus and correlates with AD severity (Fig. 1) [45, 65–67].

In addition to the Type 2 immune pathways, several other pathways have been implicated in AD. The Th1, Th22, and—to a lesser extent—Th17 cytokines may contribute to AD, although at different stages of disease. Th1 involvement tends to be most notable in chronic AD lesions, whereas the Th17 axis appears to be more prevalent in acute lesions and becomes attenuated in chronic lesions [68–71]. Th1 contributes to the chronic inflammation of AD and may also contribute to epidermal thickening [72]. The clinical significance of the modest Th17 expression in AD biology remains unclear despite several published studies on this topic [26, 68, 69, 73–75]. In addition, Th22 cells, which are characterized by IL-22 without IL-17 production, induces STAT3 activation in keratinocytes and leads to epidermal thickening characteristic of chronic AD [46, 73, 76]. Notably, the magnitude of tissue IL-22 expression in AD lesions correlates with disease severity [46].

3 AD Pipeline: Targeted Therapies

We identified completed and ongoing clinical trials of new therapies for AD by searching on the clinicaltrials.gov website. We recognize that a number of other drugs are being considered for development as AD therapies, but we limited this review to only those that are registered on the aforementioned website. We think it is worth noting that, although these newer and more targeted therapies are an advancement, the term ‘targeted’ is in fact a spectrum because a ‘target’ may in fact have many downstream actions, some of which are the intended effects whereas others may still be unintended and potentially detrimental. Space constraints have led us to focus this review primarily on therapies that are directed at normalizing the immune deviation observed in AD (Table 1). Although these treatments are more mature, we remain hopeful that therapies aimed at alleviating pruritus as well as repairing the skin barrier will hold great promise; therefore, we present these in Table 2 (anti-pruritics) and Table 3 (skin barrier repair).

A number of other anti-inflammatory therapies are in various stages of development for patients with other allergic diseases, and because of the similarities in

Table 1 Emerging treatments for atopic dermatitis

Name of agent	Route	Mechanism	Phase	NCT ID
Dupilumab	SC	Anti-IL-4R α mAb (blocks both IL-4 and IL-13 activity)	III	NCT02260986
Lebrikizumab	SC	Anti-IL-13 mAb	II	NCT02340234
Tralokinumab	SC	Anti-IL-13 mAb	II	NCT02347176
Secukinumab (Cosentyx)	SC	Anti-IL-17A mAb	II	NCT02594098
Omalizumab	SC	Anti-IgE mAb	II	NCT02300701
Ligelizumab (QGE031)	SC	Anti-IgE mAb	II	NCT01552629
MEDI4212	SC/IV	Anti-IgE mAb, with additional interaction with Fc γ RIIIa	I	NCT01544348
XmAb7195	IV	Anti-IgE mAb, additional interaction with Fc γ RIIb	Ib	NCT02148744
Tofacitinib (Xeljanz [PO])	Topical (ointment), PO ^a	JAK 1/3 inhibitor (small molecule)	II	NCT02001181
Baricitinib	PO	JAK 1/2 inhibitor (small molecule)	II	NCT02576938
PF-04965842	PO	JAK 1 inhibitor (small molecule)	IIb	Not registered yet
Ustekinumab (Stellara)	SC	Anti-IL-12/IL-23 (small molecule)	II	NCT01806662
Fezakinumab (ILV-094)	SC	Anti-IL-22 mAb	II	NCT01941537
Nemolizumab (CIM-331)	SC	Anti-IL-31RA mAb	II	NCT01986933
BMS-981164	SC	Anti-IL-31 mAb	I	NCT01614756
MEDI9929 (AMG 157)	SC	Anti-TSLP mAb	II	NCT02525094
SB011	Topical (emulsion)	DNAzyme that cleaves GATA-3	II	NCT02079688
Apremilast	PO	PDE-4 inhibitor (small molecule)	II	NCT02087943
Roflumilast	Topical (cream)	PDE-4 inhibitor (small molecule)	II	NCT01856764
Crisaborole (AN-2728)	Topical (ointment)	PDE-4 inhibitor (small molecule)	III	NCT02118792 NCT02118766
E6005	Topical (ointment)	PDE-4 inhibitor (small molecule)	II	NCT01461941 NCT02094235
OPA-15406	Topical (ointment)	PDE-4 inhibitor (small molecule)	II	NCT02068352
DRM-02	Topical (gel)	PDE-4 inhibitor	II	NCT01993420
LEO29102	Topical (cream)	PDE-4 inhibitor	II	NCT01037881
Fevipirant (QAW039)	PO	CRTH2 antagonist (small molecule)	II	NCT01785602
OC459 (OC000459)	PO	CRTH2 antagonist (small molecule)	II	NCT02002208
BBi-5000	PO	CRTH2 antagonist (small molecule)	I	NCT02590289
MRX-6	Topical (cream)	sPLA2 inhibitor (small molecule)	II	NCT02031445
AQX-1125	PO	SHIP1 activator (small molecule)	II	NCT02324972
AM1030	Topical (cream)	5-HT2BR antagonist	II	NCT02379910

5-HT2BR 5-hydroxytryptamine (2B) receptor, CRTH2 chemoattractant receptor-homologous molecule expressed on Th2 cells, DNAzyme deoxyribozyme, Fc crystallizable region of an immunoglobulin, Fc γ RIIb low-affinity Ig Fc gamma receptor subtype IIb (also called CD32), Fc γ RIIIa low-affinity Ig Fc gamma receptor subtype IIIa (also called CD16a), GATA3 transcription factor, master regulator of Th2 immune responses, Ig immunoglobulin, IL interleukin, IL-17A subtype A of IL-17, IL-31RA IL-31 receptor A, IL-4R α IL-4 receptor alpha subunit, IV intravenous, JAK Janus kinase, mAb monoclonal antibody, PDE phosphodiesterase, PO oral, SC subcutaneous, SHIP SH2-containing inositol-5'-phosphatase, sPLA2 secretory phospholipase A2, TSLP thymic stromal lymphopoietin

^a The PO formulation was tested and demonstrated efficacy in a small open-label study ($n = 6$) which was not registered on ClinicalTrials.gov [61]

pathophysiology among atopic disorders we have included these in Table 4. Of special interest in this group are the drugs targeting the cytokine IL-5 (mepolizumab, reslizumab, benralizumab, and TPI ASM8). IL-5 is observed in allergic inflammation and is thought to be produced by mast cells, eosinophils, Th2 cells, and ILC2 cells [77]. The eosinophilia observed within the tissue and blood compartments in AD subjects is thought to be

due to the actions of IL-5. Of these anti-IL-5 biologics, only mepolizumab had been studied in subjects with AD and it failed to achieve significant improvement in the primary endpoint; however, this study may have been flawed, as only two doses of mepolizumab were administered [78]. With the US FDA approval of mepolizumab for severe eosinophilic asthma in November 2015, and based on the unusually short

Table 2 Anti-itch therapies^a

Name of agent	Route	Mechanism	Phase	NCT ID
CT327	Topical (ointment)	TrkA antagonist	II	NCT01808157
VLV-686 ^b	PO	NK1-R antagonist	II	NCT02004041
DNK333	PO	NK1/NK2-R antagonist	II	NCT01033097
TS-022 ^b	Topical (lotion)	DP1-R agonist	II	NCT00914186
PAC-14028	Topical (cream)	TPRV1 channel antagonist	II	NCT02583022
ZPL-3893787	Topical	H ₄ -R antagonist	II	NCT02424253
Asimadoline (EMD-61753)	PO	κ-Opioid-R agonist	II	NCT02475447
WOL071-007 ^b	Topical (cream)	κ-Opioid-R agonist	I	NCT02576093
Clonidine + naltrexone	PO	Reduction of sympathetic outflow and opioid receptor antagonism	I	NCT02268448

AD atopic dermatitis, *DP1-R* prostaglandin D2 receptor 1, *H₄-R* histamine H4 receptor, *NK* neurokinin, *PO* oral, *R* receptor, *TPRV1* transient receptor potential cation channel subfamily V member 1, *TrkA* tropomyosin receptor kinase A, also called high affinity nerve growth factor receptor

^a All of these agents are in clinical trials for AD. However, many are also in clinical trials for other conditions

^b Thus far only being tested for atopic dermatitis per ClinicalTrials.gov

Table 3 Barrier repair therapies

Name of agent	Route	Mechanism	Phase	NCT ID
BPR277	Topical (ointment)	Kallikrein-related peptidase inhibitor	I	NCT01428297
BRT-FC-83C	Topical (cream)	Unknown	II	NCT00883311
Oregano ointment	Topical (ointment)	Antimicrobial and anti-inflammatory properties	NA ^a	NCT02289989
Holly mangrove shower gel	Topical (shower gel)	Unknown	III	NCT02178215
DS107G	Topical (ointment)	Omega-6 fatty acid derivative	II	NCT02211417
Cis-urocanic acid	Topical (cream)	Restoration of acidic pH in atopic skin	II	NCT01320579
EHK02-01 ectoine cream	Topical (cream)	Ectoine is a natural product produced by some bacteria and functions as an osmolyte	NA ^a	NCT01079897
HL-009 liposomal gel	Topical (gel)	Anti-inflammatory properties	II	NCT01568489

NA not applicable

^a Natural products that do not require FDA-approval before marketing and are exempt from the phases of drug development

treatment course in the original AD trial, there is renewed interest in studying this drug for an eosinophil-rich AD sub-phenotype [79, 80].

In addition, Table 5 contains several agents that block IL-4 and/or IL-13 activity that were studied in phase I and/or II trials for asthma ± AD but never progressed further [81–87]. Some of these agents (altrakinept [IL-4 receptor antagonist], pascolizumab [anti-IL-4], anrukinzumab [IL-13 receptor antagonist], and pitrakinra [Aeroderm; IL-4 and IL-13 antagonist]) may have failed due to subject selection and thus may warrant reconsideration with a more refined clinical phenotype or endotype [53]. Altrakinept and pitrakinra may have been more effective as an asthma therapy if they had been administered systemically rather than inhaled to improve bioavailability [53]. Lastly, a number of miscellaneous treatments (including agents of unknown mechanism, light therapies, dietary supplements,

bath additives, clothing, and topical agents) are included in Table 6.

3.1 Anti-Interleukin (IL)-4 and/or Anti-IL-13

3.1.1 Dupilumab

Dupilumab is a humanized monoclonal antibody (mAb) directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a common subunit for the type 1 and type 2 receptors that mediate most of the biological functions of the prototypic Th2 cytokines, IL-4 and IL-13. It is the first biologic therapy for adults with moderate to severe AD to undergo phase III studies. Dupilumab treatment has led to significant improvements in disease severity as measured by the Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) [88, 89]. Participants also

Table 4 Therapies being studied for atopic dermatitis-related diseases

Name of agent	Mechanism	Disease studied
Quilizumab	Binds B-cell membrane-bound IgE to prevent B-cell proliferation and differentiation	Chronic urticaria, asthma
Mepolizumab	Anti-IL-5 mAb	Asthma ^a , chronic obstructive pulmonary disease, eosinophilic esophagitis, Churg–Strauss syndrome, hypereosinophilic syndrome, bullous pemphigoid
Reslizumab	A fucosylated anti-IL-5R mAb	Eosinophilic esophagitis, asthma with elevated eosinophils, loa loa infection
Benralizumab	Anti-IL-5R mAb	Asthma, hypereosinophilic syndrome
TPI ASM8	Anti-sense oligonucleotides directed against the common beta chain of the IL-3/IL-5/GM-CSF receptors and the chemokine receptor CCR3	Asthma

CCR3 C–C chemokine receptor type 3, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *IgE* immunoglobulin E, *IL* interleukin, *IL-5* IL-5 receptor, *mAb* monoclonal antibody

^a Received FDA approval (Nov 2015) for adults and adolescents with severe asthma with an eosinophilic phenotype

Table 5 Th2-blocking therapies no longer in development for atopic disorders

Name of agent	Route	Mechanism	Phase	NCT ID
Altrakincept	Inhaled (nebulized)	Recombinant soluble IL-4R α (decoy receptor)	II	NCT00017693
Pascolizumab	SC	Anti-IL-4 mAb	I/II	NCT00024544
Anrukinzumab (IMA-638)	SC	Anti-IL-13 mAb	II	NCT00425061
IMA-026	SC	Anti-IL-13 mAb	I	NCT00725582
Pitrakinra ^a	SC, inhaled	Recombinant IL-4 variant; prevents assembly of type I and type II receptors	Ila (for AD) Iib (for asthma)	NCT00676884; NCT00801853
AMG317	SC	Anti-IL-4R α mAb	II	NCT00436670

AD atopic dermatitis, *IL* interleukin, *IL-13R α* IL-13 receptor alpha subunit, *IL-4R α* IL-4 receptor alpha subunit, *mAb* monoclonal antibody, *SC* subcutaneous

^a Pitrakinra is the only agent in this table studied for both asthma and AD

experienced a marked and early reduction in pruritus, as measured by the Numerical Rating Scale (NRS) and the 5-D pruritus scale. EASI scores significantly decreased by week 2 of treatment and reached maximal reduction by week 7 (with a mean reduction in EASI of >75 %), with improvements in itch paralleling improvements in EASI scores. The drug was well-tolerated with no serious adverse events, and only a few adverse events were observed more commonly than in placebo-treated subjects, including nasopharyngitis, conjunctivitis, headache, herpes viral infections, and injection site reactions [88, 89]. Moreover, the lesional tissue transcriptome of subjects with AD treated with dupilumab for only 4 weeks appeared to normalize (e.g., approximating that seen in non-lesional skin), and this was particularly notable for epithelial genes. This preliminary observation suggests that inhibiting the Th2 pathway may help normalize the epithelial dysfunction characteristic of this skin disorder and in so doing improve disease severity and symptomatology [90]. A decrease in serum thymus and activation-

regulated chemokine (TARC, CCL17) and tIgE was also observed in the treatment group. Interestingly, the clinical efficacy of dupilumab treatment was observed in subjects with AD regardless of their levels of serum Th2 biomarkers at study entry (e.g., tIgE, eosinophil counts, or TARC), strongly suggesting that this therapy would be effective in both the extrinsic and intrinsic AD sub-phenotypes. Phase III studies are almost completed that will address long-term safety and efficacy, and phase II studies in the adolescent population (aged 12–18 years) have begun enrollment in Europe and will likely be initiated in the USA by the second quarter of 2016. Dupilumab has also demonstrated efficacy in adult patients with asthma who were refractory to the standard of care and who had modest eosinophilia [91]. In addition, dupilumab is now being studied for other indications, including chronic sinusitis with nasal polyps and eosinophilic esophagitis, with publications suggesting that several other diseases may be considered in the future (e.g., pemphigus vulgaris, food allergy) [92, 93].

Table 6 Miscellaneous agents under investigation for treatment of atopic dermatitis

Name of agent	Route	Mechanism	Phase	NCT ID
Photocil	Topical (cream)	Sunscreen selectively allowing penetration of NB-UVB	Unknown	NCT01992172
PH-10	Topical (hydrogel)	Via photochemical reactions	II	NCT00690807
Extracorporeal photopheresis	Apheresis	Via photochemical reactions	NA ^a	NCT02226068
Blue light	NA	Via photochemical reactions	NA ^a	NCT02002871
Vitamin D	PO	Multiple cytokine modulating effects	NA ^a	NCT02058186
Omiganan (CLS001)	Topical (gel)	Cationic antimicrobial peptide	II	NCT02456480
DPK-060	Topical (ointment)	Cationic antimicrobial peptide	I, II	NCT01522391
Probiotics	PO (dietary supplement)	Immunomodulatory properties	III	NCT01500941 (various others)
Omega-3 LCPUFA	PO (dietary supplement)	Anti-inflammatory properties	NA ^a	NCT01473823
Autologous microbiome transplant	Topical (moisturizer)	Antimicrobial properties	II	NCT02144142
Dilute sodium hypochlorite (bleach) baths	Topical (bath water)	Antimicrobial properties	NA ^a	NCT01996150 (various others)
Dilute acetic acid (vinegar) baths	Topical (bath water)	Antimicrobial properties	NA ^a	NCT02582788
Lyocell/chitosan/ceramide textile	Clothing	Antimicrobial properties	II	NCT02224950
ASB17061	PO	Chymase inhibitor	II	NCT01756898
SUN13834	PO	Chymase inhibitor	II	NCT00717769
Furestem-AD	Injection	Multiple cytokine-modulating effects	II	NCT01927705
Mapracorat (ZK245186)	Topical (ointment)	SEGRA	II	NCT01359787
GW870086X	Topical (cream)	SEGRA	II	NCT01299610
Allergen-specific immunotherapy with house dust mite extract	Sublingual	Multiple cytokine modulating effects	II	NCT01471119
IgE immunoadsorption	Apheresis	Removal of IgE in blood	II	NCT02365246
PDI-192	Topical (foam)	Unknown	II	NCT01826461
LEO39652	Topical (cream)	Unknown	I	NCT02219633
LEO 32731	Topical (cream)	Unknown	I	NCT02496546
Q301	Topical (cream)	Unknown	II	NCT02426359
Ganoderma tea	PO (dietary supplement)	Unknown	I, II	NCT02533635
CNT07160	IV (infusion)	mAb of unknown target	I	NCT02345928
Benvitamod (GSK2894512, WBI-1001)	Topical (cream)	Small-molecule drug of unknown target	II	NCT02564055
KHK4577	PO	Small-molecule drug of unknown target	II	NCT02004119

IgE immunoglobulin E, *IV* intravenous, *LCPUFA* long-chain polyunsaturated fatty acids, *mAb* monoclonal antibody, *NA* not applicable, *NB-UVB* narrow-band UVB, *PO* oral, *SEGRA* selective glucocorticoid receptor antagonist

^a Natural and non-pharmaceutical products that do not require FDA-approval before marketing and are exempt from the phases of drug development

3.1.2 Lebrikizumab

Lebrikizumab is a humanized mAb directed against IL-13 that is in phase III trials for AD (NCT02340234). It has been evaluated as a treatment for asthma, with encouraging results. Subjects receiving lebrikizumab had reduced frequency of asthma exacerbations as well as

improved physiological lung function as indicated by increased forced expiratory volume in 1 s (FEV₁) [94]. The greatest efficacy was observed in patients with asthma who had the highest serum levels of a Th2 biomarker called periostin [95]. Preliminary reports from two completed phase III trials in severe asthma suggest that only one of these two studies met the primary endpoint,

namely a significant reduction in asthma exacerbations [149]. It remains to be seen how effective this drug is for AD and whether a high Th2 sub-phenotype will be more responsive as was noted in the asthma trials. One might hypothesize that blockade of both IL-4 and IL-13 actions would be more effective than targeting only one cytokine as lebrikizumab does, but other factors may also affect efficacy, such as potency, bioavailability, and pharmacokinetics of the biologic agent. Additionally, although IL-4 and IL-13 share many biological actions, IL-13 has been shown to be potentially more important in a murine model of AD [95]. Although a direct comparison of anti-Th2 therapies is unlikely to happen in the near future (if ever), it is interesting to note that, in separate studies of subjects with uncontrolled asthma (despite the use of inhaled steroids), lebrikizumab resulted in an 81 % reduction in asthma exacerbations in patients with asthma and high levels of periostin compared with an 87 % reduction in dupilumab-treated subjects with high levels of eosinophils (≥ 300 cells per microliter) [94].

3.1.3 Tralokinumab

Tralokinumab is a humanized mAb directed against IL-13 that has completed enrollment in a phase II AD trial (NCT02347176); no results have been published as yet. However, findings from a phase II trial in patients with asthma that was poorly controlled with inhaled steroids was published; it did not achieve significant improvement in the primary endpoint, the 6-item Asthma Control Questionnaire (ACQ6) [96]. However, there was a significant decrease in β_2 -agonist use and a nearly significant increase in FEV₁. Post hoc analysis in patients with high levels of sputum IL-13 at baseline demonstrated that this group had significant improvement in their ACQ6 scores and FEV₁ compared with those with low levels, which suggests that tralokinumab may be most effective in the more Th2-polarized asthma sub-phenotype, as was noted for lebrikizumab [96]. It has also been studied for refractory ulcerative colitis and chronic obstructive pulmonary disease (COPD), but no significant improvement was observed in the clinical outcomes when it was administered as an add-on therapy [97, 98]. Tralokinumab is also being studied as a treatment for idiopathic pulmonary fibrosis [99].

3.2 Anti-IL-17A

Secukinumab is an mAb directed against IL-17A, which was FDA approved for the treatment of adults with moderate to severe plaque psoriasis in January 2015 and for those with ankylosing spondylitis and psoriatic arthritis in January 2016. A small phase II clinical AD trial has been registered on the clinicaltrials.gov website, but enrollment had not

begun at the time of writing (NCT02594098). This study will enroll equal numbers of subjects with intrinsic and extrinsic AD, with the rationale that the intrinsic group may be more responsive to an anti-IL-17A therapy as they show greater activation of Th17 cells [26]. In general, secukinumab seems to be well tolerated, but reports of infections were increased, especially oral and skin candida infections as well as neutropenia [100]. Some AD thought leaders have voiced concerns about an anti-IL-17 strategy in AD because patients with AD are frequently colonized or infected with *S. aureus* on their skin. Furthermore, patients with one of two eczema-like genodermatoses, namely the autosomal dominant variant of hyper-IgE syndrome due to STAT3 deficiency or STAT1 gain of function, have an impaired production of IL-17 and experience candidal and *S. aureus* infections [101]. Secukinumab is also being investigated as a treatment for rheumatoid arthritis (RA), psoriatic arthritis, multiple sclerosis, and uveitis [102–106].

3.3 Anti-Immunoglobulin E

3.3.1 Omalizumab

Omalizumab is a humanized anti-IgE mAb that binds to the constant region of free IgE and downregulates the expression of FcεRI (on basophils, eosinophils, mast cells, and DCs) by decreasing free IgE levels [107]. It is FDA approved for the treatment of adolescents and adults with steroid-dependent allergic asthma (2003) or antihistamine-unresponsive chronic idiopathic urticaria (2014). Omalizumab has not shown efficacy for AD in a randomized, placebo-controlled, double-blinded study, although results from a number of case series have been conflicting [108–112]. A phase II study is currently enrolling to evaluate the efficacy and safety of omalizumab in children (aged 4–19 years) with severe recalcitrant AD (NCT02300701). Given that some patients with severe disease improve with omalizumab, it remains uncertain whether this therapy should be considered for off-label use in adolescents or adults for whom other systemic therapies have been ineffective or too toxic, or in AD subjects who also experience steroid-dependent allergic asthma. The unclear efficacy of omalizumab coupled with some rare but serious adverse events, such as anaphylaxis, cardiovascular and cerebrovascular events, and uncertainties about the potential risk of cancer, may limit its usefulness in AD.

3.3.2 Ligelizumab (QGE031)

Ligelizumab is an anti-IgE mAb that has higher affinity for IgE than omalizumab and has demonstrated greater reductions in free IgE in atopic patients as well as greater attenuation of the skin prick test response to allergens

[113]. A phase II trial in adult AD patients with moderate to severe disease has completed enrollment, but results are not yet available (NCT01552629) and it is unclear whether development for use in AD will continue. Ligelizumab is also in phase II development for allergic asthma, bullous pemphigoid, and projected for chronic idiopathic urticaria.

3.3.3 *Medi4212*

MEDI4212 is an anti-IgE mAb that also has higher affinity for IgE than omalizumab and—because of alterations in the crystallizable region (Fc) of the mAb—it has enhanced affinity for the Ig receptor FcγRIIIa (CD16a). This latter modification would help eliminate IgE-expressing B cells through antibody-dependent cell-mediated cytotoxicity. A phase I dose-escalation safety study that compared MEDI4212 with both omalizumab and placebo has completed enrollment (NCT01544348). Preliminary results show that a single dose of MEDI4212 (5–300 mg) reduces serum free IgE at rates similar to or better than those for omalizumab. However, it seems that at these concentrations, MEDI4212 causes more adverse events (although none were considered serious) than omalizumab.

3.3.4 *XmAb7195*

XmAb7195 is an anti-IgE mAb whose antigen-binding region (Fab) is directed against free IgE and whose Fc region is directed against the low-affinity Ig Fc gamma receptor (FcγRIIB, CD32) on T cells. This receptor prevents Th cells from stimulating B-cell differentiation into plasma cells. Thus, XmAb7195 not only binds and sequesters free IgE to prevent it from binding the high-affinity FcεRI on basophils, mast cells, DCs, and eosinophils, but it also suppresses formation of IgE-expressing plasma cells [114]. Moreover, a third mechanism of action has been described in which the IgE-XmAb7195 complex is rapidly cleared when bound to FcγRIIB on T cells. A phase Ib study is currently recruiting adult subjects with AD, allergic rhinitis, or allergic conjunctivitis (NCT02148744).

3.4 Janus Kinase Inhibitors

The JAK family consists of JAK 1, JAK 2, JAK 3, and tyrosine kinase 2 (Tyk2), all of which have tyrosine kinase activity and, upon activation, activate one or more STAT family members, which subsequently induce cellular gene expression (Fig. 2) [115]. This is an important signaling mechanism for many immune-regulation pathways, including that of many cytokines and growth factors. Therefore, JAK inhibitors block inflammation ‘from inside the cell’ as compared with anti-cytokine or anti-cytokine-

receptor agents, which block inflammation ‘from outside the cell’.

3.4.1 *Tofacitinib*

Tofacitinib is a small molecule that inhibits the JAK1 and 3 enzymes and interferes with the JAK-STAT pathway important for lymphocyte activation. A phase II study with an ointment formulation has been completed in 69 adult subjects with mild to moderate AD (NCT02001181). Preliminary results are available on clinicaltrials.gov and demonstrate an 81.7 % drop in baseline EASI score after 4 weeks of twice-daily (bid) application compared with 29.9 % in the placebo group ($p < 0.0001$), with an acceptable safety profile. An oral form of tofacitinib (5 mg bid or once daily [od]) was studied in six adult subjects with moderate to severe AD as add-on therapy to topical treatments and resulted in reductions in Scoring Atopic Dermatitis (SCORAD) values and no adverse events [116]. An oral formulation of tofacitinib currently approved for patients with moderate to severe RA who do not respond to methotrexate has shown efficacy in phase III trials for psoriasis (NCT01276639) [117]. The main adverse events from long-term use observed in patients with RA are infections, laboratory alterations (reduced neutrophil and lymphocyte counts and increased lipid and creatinine levels), diarrhea, and rare reports of lymphoma [117].

3.4.2 *Baricitinib*

Baricitinib (LY3009104) is a small molecule that inhibits JAK1 and 2 signaling. Phase II trials are currently being planned for adults with moderate to severe AD (NCT02576938). It is an oral od formulation that has shown efficacy for the treatment of patients with RA who are unresponsive to methotrexate in phase II and may also be beneficial for alopecia areata [118, 119]. A few serious infections and reductions in neutrophil counts and hemoglobin levels were observed in the RA trial, but no malignancies were reported [118]. Baricitinib is currently in phase III trials for RA (NCT02265705), phase II trials for diabetic kidney disease (NCT01683409), and compassionate use trials for several orphan diseases (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature [CANDLE], juvenile dermatomyositis [JDM], and stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy [SAVI]) (NCT01724580).

3.4.3 *PF-04965842*

PF-04965842 is a JAK1 inhibitor that has completed phase I studies and is recruiting sites for phase IIb studies to test the efficacy of this therapy for adults with moderate to

severe AD. The planned studies have not been registered on clinicaltrials.gov at the time of writing; however, the authors have received notice of them from the pharmaceutical company conducting the study. No results from the phase I studies have been published to date. The development of this drug for treatment of patients with moderate to severe psoriasis or subjects with lupus vulgaris has been discontinued.

3.5 Anti-IL-12/IL-23

3.5.1 Ustekinumab

Ustekinumab is an mAb directed against the p40 protein subunit, which is present in both IL-12 and IL-23 cytokines and therefore disrupts the progression of the Th1 and Th17 inflammatory immune responses. Although AD is thought to be predominately a disease initiated by Th2 cells, there is also a Th1 component, which is most notable in the chronic phase, and some reports have identified modest increases in Th17 cells in the peripheral blood and tissues of subjects with AD, especially the intrinsic type [26, 68, 72, 75]. This provides a rationale to consider treatment of subjects with particularly chronic, intrinsic AD with ustekinumab. Case reports have demonstrated variable efficacy in subjects with AD [120–122]. A phase II trial evaluating efficacy in adults with severe AD has finished enrollment in Japan, but no results are available yet (NCT01945086), and a pilot study in adult subjects with moderate to severe AD for whom systemic treatments have failed is registered but not recruiting (NCT01806662). Ustekinumab is FDA approved for the treatment of adults with moderate to severe plaque psoriasis (2009) and more recently for psoriatic arthritis (2013) and is now being studied in adolescents with psoriasis (NCT01090427). It is also currently in phase III trials for Crohn's disease (NCT01369355), spondyloarthropathies (NCT02407223), and ulcerative colitis (NCT02407236) and phase II trials for systemic lupus erythematosus (NCT02349061). The most common side effects from ustekinumab have been injection site reactions, cold symptoms (including reactivation of latent infections such as tuberculosis), headache, and fatigue. It is worth noting that, of the commonly used systemic or biological treatments for psoriasis, ustekinumab had the lowest rate of serious infections [123].

3.6 Anti-IL-22

3.6.1 Fezakinumab (ILV-094)

Fezakinumab (ILV-094) is an mAb directed against IL-22, thought to come from both Th22 and Th17 cells. Th22 cells are increased in AD lesions, and levels reflect disease

severity [46, 74]. Recruitment of adult subjects with moderate to severe AD is ongoing for a phase II study (NCT01941537). It has previously been studied for treatment of adults with psoriasis (NCT00563524) and RA (NCT00883896), but these indications are no longer being pursued.

3.7 Anti-IL-31/Anti-IL-31R

3.7.1 Nemolizumab

Nemolizumab (CIM331) is an mAb that targets the IL-31 receptor A (IL-31RA). IL-31 acts through a heterodimeric receptor composed of IL-31RA and the oncostatin M receptor (OSMR), which are expressed on keratinocytes, eosinophils, and neurons that coexpress transient receptor potential cation channel vanilloid subtype 1 receptors (TRPV1) [124]. It is released by activated Th cells (especially Th2), mast cells, and mononuclear cells and is thought to mediate itch in a number of conditions, including AD, prurigo nodularis, and cutaneous T-cell lymphoma [48, 67, 125]. In a phase I/II trial, nemolizumab was well tolerated, and subjects with AD experienced a 50 % reduction in itch as assessed by the pruritus visual analog scale (VAS) after 4 weeks of treatment compared with 20 % for placebo [126]. There were no serious adverse events, but an increase in creatine phosphokinase was more common in the nemolizumab group. Enrollment has now been completed for a phase II study in adults with moderate to severe AD where the primary outcome was improvement in pruritus (NCT01986933). No published data are available from this study.

3.7.2 BMS-981164

BMS-981164 is an mAb directed against IL-31. It has completed a phase I trial in healthy individuals and adults with moderate to severe AD. The results from this early-phase study have not yet been released (NCT01614756).

3.8 Anti-TSLP

MEDI9929/AMG 157 (NCT02525094) is an mAb targeting TSLP, which is an epithelial-derived cytokine produced in response to barrier disruption or innate signals and drives allergic inflammatory responses (e.g. Type 2) through its actions on a number of cells, including DCs [127]. A phase II study evaluating the effects in adults with moderate to severe AD is currently enrolling (NCT02525094). MEDI9929 also has demonstrated efficacy in reducing bronchial hyper-reactivity and sputum eosinophilia in patients with mild asthma undergoing allergen challenge in a phase I study

(NCT01405963) [128]. A phase II study in adults with severe inadequately controlled asthma has completed enrollment (NCT02054130). Recruitment is ongoing for a study of MEDI9929 in adolescents with mild to moderate asthma (NCT02512900) and in adults as adjunct therapy with cat immunotherapy to see whether this combination can induce more long-lasting cat tolerance in patients with cat sensitization (NCT02237196).

3.9 Anti-GATA-3

SB011 is a topical formulation that contains the deoxyribozyme (DNAzyme) hgd40, which cleaves GATA-3 messenger RNA (mRNA). GATA-3 is a transcription factor that activates expression of the Th2 cytokine locus, binding to multiple sites that positively regulate expression of IL-4, IL-5, and IL-13 [129]. A phase II study is currently recruiting adult subjects with mild to moderate AD (NCT02079688).

3.10 Phosphodiesterase 4 Inhibitors

Humans have 11 different phosphodiesterases (PDEs). Leukocytes from subjects with AD have elevated PDE activity and an increase in the mRNA levels of PDE4A and PDE4B2 within the T-cell compartment [130, 131]. PDE4 is the most prevalent PDE in keratinocytes and cells of the immune and nervous systems. PDEs are responsible for hydrolyzing cyclic adenosine monophosphate (cAMP); therefore, PDE inhibitors will cause accumulation of intracellular cAMP and inhibit cytokine transcription and a number of other cellular functions.

3.10.1 Apremilast

Apremilast is an oral agent that is FDA approved to treat adults with plaque-stage psoriasis and psoriatic arthritis (2014) and is in phase III trials for ankylosing spondylitis (NCT01583374) and in the preregistration phase for Behcet's disease. It is currently in phase II trials for adults with moderate to severe AD (NCT02087943) and ulcerative colitis (NCT02289417) and for adolescents with moderate to severe plaque psoriasis (NCT02576678). In 2012, two small open-label studies were published evaluating the safety and efficacy of apremilast in adult subjects with AD and/or contact dermatitis, with modest improvements observed in EASI and IGA scores [132, 133]. Although no serious adverse events were observed, patients not uncommonly reported a number of more minor adverse events, including headache, nausea, and soft stools.

3.10.2 Roflumilast

Roflumilast is a topical PDE4 inhibitor that has recently completed a phase IIa AD trial involving 20 subjects (NCT01856764). The results on the clinicaltrials.gov website demonstrate a trend toward improvement in the primary endpoint of SCORAD values along with a trend toward improvement in TEWL. The only statistically significant outcome was reduction in pruritus. An oral form of roflumilast was FDA approved for severe COPD in 2011, and this formulation has also demonstrated efficacy in asthma and allergic rhinitis [134, 135]. Similarly, this oral formulation is in development as add-on therapy for type 2 diabetes mellitus (NCT01664624), schizophrenia (NCT02079844), polycystic ovary syndrome (NCT02037672), sarcoidosis (NCT01830959), and memory impairment (NCT02051335). It is no longer being studied for nonalcoholic steatohepatitis.

3.10.3 Crisaborole

Crisaborole (AN-2728) is a boron-containing topical PDE4 inhibitor, for which three phase II trials in adolescents and adults have been published [136–139]. Results from the largest of these, a dose-justification study that enrolled adolescents, observed that bid application of crisaborole 2 % ointment resulted in total or partial clearance of target lesions in 62 % of subjects after 29 days of treatment and a 71 % reduction in the Atopic Dermatitis Severity Index (ADSI) score [136]. In the phase IIa adult study, 68 % experienced a decrease in ADSI in the crisaborole-treated lesion compared with only 20 % in the vehicle-treated lesion [137]. The phase IIa open-label adolescent study demonstrated that >70 % of subjects achieved an Investigator's Static Global Assessment (ISGA) score of 0 or 1 (clear or almost clear) with crisaborole [138, 139]. Two post hoc pooled analyses of the four studies found that >80 % of subjects experienced a categorical shift of pruritus intensity (0–1.5 = no—mild, 2–3 = moderate—severe) at the earliest post-baseline efficacy assessment (day 8 or 15, depending on the study), and this effect was maintained for the duration of the study [140]. Crisaborole 2 % is generally well-tolerated, with the most common adverse effects being application site reactions, nasopharyngitis, and upper respiratory tract infections. The common side effects of the systemic PDE4 inhibitors (nausea, vomiting, and headache) were not observed for this topical medication, and serum drug concentration studies show that it is not absorbed systemically to any significant extent. The drug has recently completed two phase III trials in children and adults with mild to moderate AD (NCT02118792, NCT02118766), and a press release from the pharmaceutical company reported that approximately 32 % of patients achieved a score of 0 or 1 in the ISGA as compared with only 18–25 % of vehicle-treated patients [141].

3.10.4 E6005

E6005 is a topical PDE4 inhibitor that has completed two phase II trials in Japan, enrolling adults (NCT01461941) or children (NCT02094235) with mild to moderate AD. Published data from the adult trial demonstrated a trend of clinical improvement after 4 weeks of bid applications in all AD severity measures, but none reached significance. An additional 8-week extension (12 total weeks of treatment) resulted in modest but statistically significant improvements in EASI and SCORAD (objective and subjective) scores compared with baseline measurements [142]. Plasma E6005 was undetectable in all subjects, but very low plasma concentrations of an E6005 metabolite were detected in 47 % of subjects. No serious adverse events were reported, but some patients experienced application site edema and erythema as well as increased alanine aminotransferase levels [143].

3.10.5 Opa-15406

OPA-15406 (NCT02068352) recently completed a phase II trial enrolling subjects aged 10–70 years with mild to moderate AD, with randomization to bid application of 1 %, 0.3 %, or vehicle ointment. The primary endpoint of success (IGA of 0 or 1 with ≥ 2 -grade reduction) was met in the 1 % group at week 4. The mean percentage improvement in EASI was statistically significant in the 1 % group by the end of week 1 (31.4 vs. 6 % for vehicle), continued to increase in week 2 (39.0 vs. 3.0 % for vehicle), and lasted for 8 weeks [144]. Pruritus VAS improvement was also statistically significant in the 1 % group during week 1. AEs deemed potentially related to study treatment included worsening AD, application site reactions, and vulvovaginal yeast infection; none of which were considered serious.

3.10.6 DRM-02 and LEO29102

DRM-02 (NCT01993420) and LEO29102 (NCT01037881) are additional topical PDE4 inhibitors that have completed phase II trials in AD, but the results of these studies have not yet been published. DRM-02 is also being tested for its efficacy in rosacea and psoriasis, and LEO29102 is also in development for psoriasis.

3.11 CRTH2 Antagonists

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2; also known as DP₂) is one of the two receptors that prostaglandin D₂ (PGD₂) binds to and it mediates its biological actions. PGD₂ is produced by the actions of cyclooxygenase (COX)-1 or COX2, which convert arachidonic acid (AA) into cyclic endoperoxidases,

including PGD₂. IgE-activated mast cells are the greatest cellular source of PGD₂, but DC and Th2 cells are also sources of PGD₂ [145]. PGD₂ is produced in high concentrations in response to allergen challenge; upon binding to CRTH2, it both activates and induces chemotaxis of eosinophils, basophils, and Th2 cells. In summary, in vitro and murine models suggest that CRTH2 might have an important role in the recruitment of allergic cell types and in driving Th2 cytokine production.

Fevipirant (QAW039) (NCT01785602), OC459 (NCT02002208), and BBI-5000 (NCT02590289) are oral CRTH2 receptor antagonists in development for the treatment of allergic diseases. Fevipirant has completed a phase II trial, with results available only on the clinicaltrials.gov website. Adults with moderate to severe AD were treated with either QAW039 at 450 mg per day or placebo for 12 weeks, with minimal effect on the primary endpoint of change from baseline EASI score (mean $-8.65 \pm$ standard error of the mean [SEM] 0.01 for QAW039 and -6.95 ± 0.01 for placebo [no statistics provided]). Fevipirant is still in development for asthma. OC459 (also known as OC000459) is a daily oral medication currently finishing a phase II trial in adult subjects with moderate to severe AD. OC459 is also in development for the treatment of allergic asthma (NCT01057927), allergic rhinitis (NCT01448902), and eosinophilic esophagitis (NCT01056783). BBI-5000 is still in phase I trials in healthy adults, with the expectation that the first indication will be AD.

3.12 Secretory Phospholipase A2 (sPLA2) Antagonists

Secretory Phospholipase A2s (sPLA2s) are a family of enzymes that release AA from membrane phospholipids and generate lysophospholipids [146]. sPLA2s are well-recognized for their digestive, neurotoxic, myotoxic, and anticoagulant actions, but more recently have also been shown to have proinflammatory and antibacterial activities. MRX-6 is a topical sPLA2 inhibitor being developed as treatment for mild to moderate AD (NCT02031445) and contact dermatitis (NCT00867607). A phase II study is currently recruiting children (aged 2–17 years) with mild to moderate AD to evaluate the safety and efficacy of MRX-6 2 % cream versus vehicle applied bid for 4 weeks with an open-label extension (NCT02031445).

3.13 SH2-Containing Inositol-5'-Phosphatase (SHIP)-1 Activator

SHIP1 is an endogenous inhibitor of the phosphoinositide-3-kinase (PI3 K) pathway that is involved in the activation and chemotaxis of inflammatory cells [146]. It is primarily expressed in hematopoietic cells. Therefore, a SHIP1

activator would induce a selective down-regulation of the activity of the PI3 K pathway only in hematopoietic cells.

AQX-1125 is an oral drug for oral administration being studied in a phase II trial in adults with mild to moderate AD (NCT02324972). It has also been studied in adults with mild to moderate asthma with only modest decreases in late-phase allergic responses and no significant reductions in sputum leukocytes [147]. In the asthma study, patients receiving AQX-1125 reported more frequent but mild gastrointestinal side effects (dyspepsia, nausea, and abdominal pain).

3.14 5-Hydroxytryptamine (5-HT) 2B-R Antagonist

5-HT is serotonin, which is recognized as a neurotransmitter, pruritogen, vasodilator, immunomodulator, growth factor, and inducer of epithelial proliferation [148]. The biological actions of 5-HT are mediated through seven families of membrane-bound receptors (5HT1-7R) that include at least 21 subtypes. AM1030 is a topical cream that antagonizes one of these receptors, 5-HT_{2B}R, and has been evaluated in a phase I/II study of adults with mild to severe AD (NCT02379910), but results have yet to be published.

4 Conclusion

Our enhanced understanding of AD pathogenesis has paved the way for development of more targeted therapies to improve the signs and symptoms of AD. Of the many therapies in the AD pipeline with evaluable study results, the greatest promise seems to be with drugs that inhibit the Type 2 immune responses (upstream or downstream). This highlights that the Th2 axis plays a critical role in the signs and symptoms of AD. Larger trials with the more promising drug candidates are eagerly awaited by patients, their families, and healthcare providers. Hopefully, these trials will confirm encouraging preliminary findings, refine disease phenotypes based on responsiveness, more fully explore the effects of these drugs on patient-reported outcomes, and ultimately lead to new FDA-approved treatments for the most common inflammatory skin disorder. In time, we hope to see many new systemic therapies and ultimately hope that this will - lead to head-to-head comparisons to clarify when and how to use them and how they fit into the current standard of care.

Compliance with Ethical Standards

Conflict of interest Lisa A. Beck, MD, has acted as a consultant for Abbvie, Array BioPharma, Celgene, Genentech, Janssen, Medimmune, Novartis, Regeneron, Sanofi, Stiefel/GSK, and Unilever and owns Pfizer and Medtronic stock. She is Principal Investigator for clinical trials from Genentech and Regeneron and Co-Investigator for clinical trial from Xoma. Diane Wang, MD, is Co-Investigator for clinical trials from Genentech, Regeneron and Xoma.

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