



Monoclonal antibodies for the treatment of atopic dermatitis

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Purpose of review

To evaluate the treatment revolution atopic dermatitis, the most common inflammatory skin disease, has been going through in recent years, thanks to breakthroughs in disease understanding, delineating the immune fingerprint of atopic dermatitis.

Recent findings

The treatment for moderate-to-severe atopic dermatitis patients has been largely unchanged for decades and relied on broad-acting immunosuppressants. A huge unmet need existed for effective, well tolerated and narrow-targeted therapeutics. Multiple therapies, targeting various aspects of the complex immune activation of atopic dermatitis, are now assessed in clinical trials, and hold promise for a new era in the treatment of atopic dermatitis, comparable with the treatment shift seen for psoriasis in the last decade. The first effective monoclonal antibody licensed for the treatment of atopic dermatitis, dupilumab, not only offers a much-needed systemic agent for moderate-to-severe patients but also provides strong evidence for the potential role of other monoclonal antibodies in disease management.

Summary

In this rapidly changing field, new atopic dermatitis-targeted monoclonal antibodies will be reviewed in light of the recently discovered pathomechanisms of the disease.

Keywords

atopic dermatitis, inflammatory, monoclonal antibody, targeted treatment

INTRODUCTION

Atopic dermatitis, also known as atopic eczema, is the most common inflammatory skin disease, affecting 15–25% of children and 3–7% of adults, of which 20% have moderate-to-severe disease [1–3]. Elevated IgE levels are found in up to 80% of patients ('extrinsic atopic dermatitis'), but 20% of patients have normal levels of IgE ('intrinsic atopic dermatitis') and usually lack an atopic background [4]. Approximately half of atopic dermatitis patients have other atopic manifestations (food allergies, asthma, and allergic rhinitis) [5,6].

For many years, despite its increasing prevalence, and the significant burden of the disease with substantial impairment in quality of life because of chronic pruritus, sleep disruption, and depression [7,8], there were no targeted therapies for severe atopic dermatitis patients. Disease management with broad, nonspecific immunosuppressants only provided symptomatic and temporary relief, but was associated with extensive adverse effects [9]. Thus, there is a large unmet need for safer, narrow-acting systemic therapeutics for moderate-to-severe atopic dermatitis patients.

Although in the past decade, numerous new and targeted therapies completely transformed the treatment paradigm for another, less prevalent, inflammatory skin disease, psoriasis, we are finally witnessing the rapid development of multiple therapeutics for atopic dermatitis, marking a new era. Recently, new insights on disease pathogenesis lead to development and testing of novel therapeutics [10,11]. Herein, we will review newly approved or under developed atopic dermatitis-targeted treatments (Table 1). Strategies that failed to show efficacy for atopic dermatitis, such as IgE inhibition (by

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KEY POINTS

- Atopic dermatitis is recently being under intensive research and clinical trials, redefining its longstanding clinical management once based on broad-acting immunosuppressants.
- As disease is largely Th2/Th22-skewed, attempts to find targeted therapies had largely concentrated on these immune axes, and led to the development of the first licensed monoclonal antibody for atopic dermatitis – an IL-4/IL-13 inhibitor, dupilumab.
- Other multiple monoclonal antibodies for atopic dermatitis had already shown variable efficacy in clinical trials, including anti-IL-13, anti-IL-31, anti-IL-33, anti-IL-22, anti-IL-17C, and anti-IL-23 agents, as well as broad-acting new drugs, such as JAK inhibitors.
- Future trials will delineate the new treatment paradigm for atopic dermatitis, and will establish the role of each therapeutic agent in the complex immune interplay of atopic dermatitis.

omalizumab, although other anti-IgE agents are still investigated, ClinicalTrials.gov NCT01552629) [22,23], IL-6 inhibition (by tocilizumab, improved atopic dermatitis symptoms but caused bacterial infections during treatment) [24], or tumor necrosis factor antagonism (by infliximab, adalimumab, and etanercept, may even result in atopic dermatitis exacerbations) [25–27], will not be reviewed.

ATOPIC DERMATITIS FOLLOWS THE FOOTSTEPS OF PSORIASIS

Targeted monoclonal antibodies in dermatology were first introduced for treatment of psoriasis, gaining central role in the therapeutic management as the underlying immune dysregulations were elucidated [28,29]. Although psoriasis represents the best existing model for translational studies in an inflammatory skin disease, there are some major differences with atopic dermatitis that were recently delineated, making the psoriasis model only partly applicable for atopic dermatitis [30–33].

Although both diseases are T-cell mediated inflammatory dermatoses, psoriasis is primarily Th17-skewed, atopic dermatitis is predominantly Th2/Th22-centered [30,31,33]. However, atopic dermatitis encompasses different clinical subtypes with corresponding molecular phenotypes, including Asian-origin, intrinsic, and pediatric atopic dermatitis, resulting in a more variable atopic dermatitis signature [4,34–36]. Interestingly, some findings are shared between certain atopic dermatitis subtypes and psoriasis, such as prominent acanthosis and

focal parakeratosis in Asian atopic dermatitis, as well as over-expressed Th17 [35]. These clinical and immunological similarities raise a possible view of psoriasis and atopic dermatitis as polar diseases on a shared spectrum, with some IL-17-enriched atopic dermatitis phenotypes ranging between these poles [31]. These phenotypes may necessitate targeting of more than one cytokine axis, and respond less optimally to single-cytokine antagonism.

Another significant feature of atopic dermatitis, with important clinical implications, is its systemic nature with disease evolution beyond appreciable skin lesions, as immune abnormalities also involve the uninvolved ('nonlesional') atopic dermatitis skin and blood [33,37,38]. These findings suggest further advantage for systemic approaches in patients with moderate-to-severe atopic dermatitis, and more than 10% body surface area involvement.

TH2 AS A THERAPEUTIC TARGET

Atopic dermatitis skin lesions show robust up-regulations of many Th2-related cytokines and chemokines, including IL-4, IL-5, IL-13, IL-31, CCL11, thymus and activation-regulated chemokine (TARC/CCL17), and CCL26 [33,36,39–41]. The two key Th2 cytokines, IL-4/IL-13 were suggested to drive important pathologic processes in atopic dermatitis, including recruitment of inflammatory cells to skin by up-regulating Th2-associated chemokines (i.e. CCL17 and CCL26), and inhibition of lipid synthesis, tight junction formation, antimicrobial peptides (AMPs), and differentiation of keratinocytes [42–46]. IL-4/IL-13 were also shown to induce bacterial binding and colonization, and staph infections are common in atopic dermatitis [33,44,47,48]. These cytokine effects ultimately result in both immune and barrier dysregulation characteristic to atopic dermatitis. In sum, as atopic dermatitis is largely Th2-centered, Th2-antagonism is a key potential treatment strategy for this disease.

IL-4/IL-13 ANTAGONISM

Due to the pivotal role of Th2 pathway in atopic dermatitis, it is not surprising that the first monoclonal antibody developed and licensed for the treatment of moderate-to-severe atopic dermatitis, dupilumab, antagonizes both IL-4 and IL-13 [12]. Dupilumab, a fully human monoclonal antibody, blocks both cytokines by binding to their common IL-4 receptor- α (IL-4R α). The drug showed robust clinical efficacy in randomized, double-blinded, placebo-controlled phase III studies [12,49], and molecular studies in tissues correlated clinical improvements with tissue changes, as well as with

Table 1. Monoclonal antibodies targeting atopic dermatitis-related cytokines

Immune axis	Target	Agent/trade name	Manufacturer	Results from past clinical trials	Current clinical trial phase	ClinicalTrials.gov
Th2	IL-4 and IL-13 (via IL-4R α blockade)	Dupilumab/ Dupixent	Regeneron/ Sanofi	The first licensed monoclonal antibody for atopic dermatitis treatment. Showed consistent efficacy in three phase III trials [12, 13]	Licensed for adult patients, in phase III for children	NCT02612454 (for ages 6 months to 18 years)
	IL-13 (via blockade of IL-13Rs)	Tralokinumab	AstraZeneca	Response to tralokinumab differs with DPP-4 levels in blood, with significant improvement in clinical scores in the DPP-4-high subpopulation, and numerical, nonsignificant improvement in the DPP-4-low subpopulation [14]	III	NCT03363854
	IL-13	Lebrikizumab	Hoffmann-La Roche	In a proof-of-concept study, significantly more patients achieved clinical response with lebrikizumab vs. placebo, yet study design resulted in very high response rates in the placebo group [15]	II	NCT03443024
	IL-31RA	Nemolizumab	Chugai	Marked reductions of both EASI and SCORAD scores, yet without statistical significance from placebo. Significant decrease in pruritus scores [16]	II	NCT03100344
	IL-31	BMS-981164	BMS	-	I	NCT01614756
	TSLP	Tezepelumab	Medimmune	Phase II study did not meet the primary endpoint and the drug-treated group did not improve EASI scores compared with placebo	No active clinical trials	NCT02525094
	TSIPR	MK-8226	Merck	Phase I study terminated prematurely because of financial reasons	No active clinical trials	NCT01732510
	OX40	GBR 830	Glenmark	Phase II study showed long-acting effect after two intravenous doses of the drug, coupled with significant improvements of mechanistic markers and histological findings [17]	II	NCT02683928
	IL-33	KHK4083	Kyowa Hakko Kirin	-	I	NCT03096223
		ANB020	AnaptyBio	Small, proof-of-concept, phase II clinical trial showed significant clinical efficacy over placebo [18]	No active clinical trials, but future trials are expected	-
Th22	IL-22	Fezakinumab	Pfizer	Significant improvement in clinical scores vs. placebo in severe patients, yet only numerical efficacy in SCORAD in the entire fezakinumab-treated group compared with the placebo-treated group [19]	II	NCT01941537
Th17/IL-23	IL-12/23p40	Ustekinumab/ Stelara	Janssen	Only numerical, nonsignificant improvements in clinical scores for ustekinumab over placebo [20]	No active clinical trials	-
	IL-17A	Secukinumab/ Cosentyx	Novartis	-	II	NCT02594098
	IL-17C	MOR106	MorphoSys/ Galapagos	Small, proof-of-concept phase I clinical trial showed promising response rates [21]	No active clinical trials, but phase II trials are expected	-

DPP-4, dipeptidyl peptidase 4; EASI-50: Eczema Area Severity Index improved by 50%; IL, interleukin; R, receptor; SCORAD, SCORing atopic dermatitis; TSLP, thymic stromal lymphopoietin.

reversal of characteristic epidermal disease in atopic dermatitis [50–52]. Interestingly, dupilumab not only down-regulates Th2-related markers (i.e. CCL17, CCL18, and CCL26), but also antagonizes some Th17/Th22-related markers, including IL-23p19, elafin/PI3, and S100A proteins [51].

Dupilumab was well tolerated, and adverse events mainly included injection-site reactions, nasopharyngitis, and increased rate of conjunctivitis, that its nature is unclear and has not been observed in other atopic indications for this drug, such as asthma [12,13[¶],49,52,53]. Of note, patients on dupilumab seemed to have lower rates of skin infections compared with placebo arms, probably because of improvement of epidermal barrier [12,49]. Dupilumab represents a new era in atopic dermatitis therapeutics, providing a narrow, targeted agent that reverse atopic dermatitis both clinically and molecularly.

Tralokinumab and lebrikizumab are IgG4 fully humanized monoclonal antibodies specifically antagonizing IL-13.

Tralokinumab blocks the IL-13 cytokine by binding a heterodimeric receptor, composed of IL-4R α (targeted by dupilumab) and IL-13R α 1, as well as the IL-13R α 2 decoy receptor, that lowers cytokine levels [54]. It is in phase III clinical trials for asthma and atopic dermatitis (NCT03363854). In asthma, serum dipeptidyl peptidase 4 (DPP-4), a protein derived from the bronchial epithelium, has been reported as a predictive biomarker for tralokinumab efficacy in patients with severe asthma, and exploratory analyses by stratified DPP-4 were also undertaken in atopic dermatitis trials [14,55]. Although high-placebo responses were seen in the study that allowed application of topical steroids, atopic dermatitis patients treated with tralokinumab achieved greater responses, with significant reduction in clinical atopic dermatitis scores in the DPP-4-high subpopulation, and numerical, nonsignificant efficacy in the DPP-4-low subpopulation, with an acceptable safety and tolerability profile. These findings suggest that DPP-4 may serve as a predictive biomarker for atopic dermatitis patients who may benefit from tralokinumab treatment [14].

Lebrikizumab specifically binds soluble IL-13 at an epitope that strongly overlaps with the binding site of IL-4R α [56]. It is also investigated for asthma [57], other pulmonary conditions, and for atopic dermatitis (NCT03443024). In a proof-of-concept phase II randomized, double-blinded, placebo-controlled study of lebrikizumab for atopic dermatitis, significantly more patients achieved clinical response with lebrikizumab vs. placebo at 12 weeks, yet very high response rates were found in the placebo group [82.4 vs. 62.3% achieved Eczema Area

Severity Index (EASI)-50, indicating an improvement of 50% in this clinical score] [15[¶]]. It was concluded that the study design, instructing participants to apply twice-daily topical corticosteroids before and during the trial in all study groups, might have resulted in decreased dropout rate, but impaired the ability to fully assess the efficacy of lebrikizumab in atopic dermatitis. The drug was well tolerated, as previously published in larger-scale asthma studies [57].

These data suggest exclusive IL-13-targeting may be an effective approach for atopic dermatitis, and clinical trials investigating these drugs as monotherapy, similar to dupilumab, will further dissect the role of IL-13 in atopic dermatitis, as the question whether IL-4 and IL-13 are redundant or complementary in atopic dermatitis pathogenesis, still exists.

TARGETING PRURITUS: ANTI-IL-31 THERAPIES

Another Th2 cytokine, IL-31, is significantly up-regulated in acute and chronic atopic dermatitis lesions, correlates with disease severity, and has been suggested to mediate the atopic dermatitis-associated itch [58,59]. Antihistamines in atopic dermatitis show little or no effect on itch [60], and immune molecules with pruritic effects are possible therapeutic targets. IL-31 cytokine has also been suggested to contribute to the compromised epidermal-barrier dysfunction, preserving and extending the ‘itch-scratch’ cycle of atopic dermatitis [3,59,61,62]. Nemolizumab, a humanized monoclonal antibody against IL-31 receptor A, blocks IL-31 signaling on various cells, including peripheral neurons [16[¶]]. A phase II randomized, double-blinded, placebo controlled study of nemolizumab for atopic dermatitis showed marked reductions of both EASI and SCORing atopic dermatitis (SCORAD) scores, but these changes did not reach statistical significance. The drug, however, did significantly decrease pruritus scores (63% improvement in itch compared with 21% in the placebo group at 12 weeks). No serious side effects were observed in association with nemolizumab as compared with the placebo group, with the exception of exacerbations in atopic dermatitis and peripheral edema, which were more common among patients receiving nemolizumab, but the mechanisms for these phenomena are not clear [16[¶]].

An anti-IL-31 monoclonal antibody, BMS-981164, has been studied in early clinical trials for atopic dermatitis, but did not move forward (NCT01614756). Future studies should determine whether IL-31 antagonism merely provides symptomatic, antipruritic relief, or can also modulate

atopic dermatitis disease activity, and refine the role of IL-31 antagonism in atopic dermatitis.

THYMIC STROMAL LYMPHOPOIETIN AND OX40 ANTAGONISM

Thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine, has been referred to as the ‘master switch of allergic inflammation,’ because of its role as the trigger of the downstream cascade of Th2 inflammation in asthma and atopic dermatitis [63]. TSLP drives Th2 polarization in dendritic cells, Langerhans cells, and mast cells, activates CD4⁺ T-naïve cells to produce Th2-related cytokines, and induces expression of OX40-ligand on dendritic cells [64–66]. TSLP and its receptor, TSLPR, are up-regulated in atopic dermatitis skin [4], and are therefore, potential therapeutic targets for atopic dermatitis. Nevertheless, tezepelumab, a fully human monoclonal immunoglobulin G2λ that specifically binds and inhibits TSLP, failed to show clinical efficacy in a phase II clinical trial (NCT02525094) [67]. A clinical trial investigating TSLPR antagonist for the treatment of atopic dermatitis (MK-8226, NCT01732510) was terminated because of business reasons.

Downstream to TSLP, dendritic cells expressing OX40-ligand are driven by OX40, a costimulatory receptor on activated T cells, which further intensifies Th2-skewing, contributing to the maintenance of chronic allergic inflammation [68,69]. A phase II clinical trial of an OX40 antagonist, GBR 830 (NCT02683928), showed that after two intravenous doses of the drug, a significant greater proportion of GBR 830-treated patients achieved EASI-50 as compared with placebo on day 71 – a relatively long lasting effect. In addition, significant reductions of treatment-specific biomarkers (OX40⁺ T cells, OX40-ligand⁺ dendritic cells), coupled with significant reductions in epidermal hyperplasia measures, and atopic dermatitis molecular biomarkers, were found in GBR 830-treated patients compared with the placebo group. GBR 830 was overall well tolerated [17[¶]]. Another anti-OX40 monoclonal antibody, KHK4083, is in an ongoing phase I open-label clinical trial for atopic dermatitis in Japan (NCT03096223).

An amplifier of the TSLP-OX40 axis, IL-33, is also considered a Th2 cytokine [70,71]. IL-33 is up-regulated in atopic dermatitis skin [26], and was shown to directly weaken barrier function in atopic dermatitis by down-regulating *FLG* expression [71]. IL-33 is, therefore, another therapeutic target for atopic dermatitis, as demonstrated in a murine model of atopic dermatitis, treated successfully with an anti-IL-33 agent [72]. Indeed, a small, proof-of-concept,

phase II clinical trial of an anti-IL-33 monoclonal antibody, ANB020, showed favorable clinical results in atopic dermatitis [18], and future trials are expected.

IL-5 INHIBITION

IL-5, another Th2-related cytokine up-regulated in atopic dermatitis, specifically acts on eosinophils, resulting in increased presence and activation of these cells [39,73,74]. Nevertheless, anti-IL-5 approach by a monoclonal IL-5 antagonist, mepolizumab, did not show efficacy for atopic dermatitis in an early trial [75]. Despite these preliminary disappointing results, future studies utilizing IL-5 antagonists in larger and longer clinical trials are needed to define the cytokine’s role in the pathogenesis of atopic dermatitis.

IT IS NOT ALL ABOUT TH2: BLOCKING TH22

Atopic dermatitis is not only Th2-centered among various disease subtypes, it also over-expresses Th22-related cytokines and chemokines, such as IL-22 and S100A proteins [39]. IL-22 is a key Th22 cytokine, and IL-22-producing Th22 cells are abundant in atopic dermatitis skin lesions [40,76]. IL-22 inhibits epidermal differentiation by down-regulating terminal differentiation genes (such as *loricrin* and *filaggrin*) [62,76–78], and drives the epidermal acanthosis characterizing chronic atopic dermatitis lesions [40,76]. IL-22 levels were shown to correlate with disease severity, and with clinical response following various treatments including topical steroids, cyclosporine A, phototherapy by NB-UVB, dupilumab, and ustekinumab [20,51,79–82]. These data provides a rationale for anti-IL-22 therapies in atopic dermatitis.

Fezakinumab is a human IgG1A antibody that binds IL-22 and inhibits its activity [19[¶]]. A randomized, double-blind, placebo-controlled trial with fezakinumab as monotherapy for atopic dermatitis showed numerical efficacy by SCORAD assessments in the fezakinumab-treated group compared with the placebo-treated group, but did not reach significance. However, SCORAD decline in severe patients and other clinical response scores [body surface area involvement and Investigator Global Assessment (IGA)] were significantly better in the drug-treated group [19[¶]]. Fezakinumab was well tolerated, with comparable adverse events rate between study arms. Most common adverse events were viral upper respiratory tract infections [19[¶]]. Thus, in severe patients with insufficient response to Th2 inhibition by dupilumab [12], an IL-22-antagonism approach

may hold promise. Larger future studies should allow a better understanding of the potential benefit of IL-22 inhibition in atopic dermatitis.

TH17/IL-23: ARE THEY ALSO RELEVANT TARGETS?

Th17-related cytokines, specifically IL-17 and IL-23, are the key drivers of the inflammatory process in psoriasis and are extremely effective targets for psoriasis therapeutics [29]. Although Th2/Th22 up-regulations are common across all atopic dermatitis subtypes, as mentioned above, atopic dermatitis skin lesions show also variable Th17 activation [74,83]. These up regulations include overexpression of IL-23 and IL-17 in lesional atopic dermatitis skin in comparison with normal skin, but overall levels are lower as compared with psoriatic skin [83]. Several atopic dermatitis subtypes show higher IL-17/IL-23 activation [4,35,36]. IL17 synergizes with IL-22 to promote tissue inflammation and barrier defects, and IL-23 induces both Th17 and Th22 [84]. Significant decreases in IL-23 were found in atopic dermatitis skin following treatment with topical and systemic agents, including topical steroids, phototherapy (NB-UVB), cyclosporine A, and dupilumab [51,79–82]. These findings support a rationale for IL-23 and IL-17 as potential therapeutic targets for atopic dermatitis.

IL-23 is composed of two subunits, and ustekinumab, a human monoclonal IgG1 antibody, binds and inhibits the shared p40 subunit of IL-12 and IL-23. The other subunit, IL-23p19 is unique for IL-23 [85]. Ustekinumab is highly efficacious in psoriasis because of its IL-23 antagonism [86,87]. A phase II, double-blind, placebo-controlled clinical trial of ustekinumab for atopic dermatitis showed robust immune modulation consistent with disease molecular response. However, only numerical improvements in clinical scores for ustekinumab over placebo were obtained, as decline in scores did not reach statistical significance [20]. It was concluded that the lack of significance could be contributed to the use of topical steroids and inadequate dosing of ustekinumab, and future larger trials are needed [20].

The IL-17 family consists of six members, IL-17A through IL-17F [88]. IL-17A inhibition was well investigated in psoriasis, and the substantial efficacy of IL-17A inhibitors had elucidated the crucial role Th17 has in psoriasis [89]. Inhibition of IL-17A in psoriasis suppresses not only the expression of downstream cytokines and inflammatory components, but also upstream gene expressions are inhibited, including IL-23 [28,90]. For atopic dermatitis, a randomized placebo-controlled phase II clinical trial

of secukinumab, a recombinant, high-affinity, fully human IgG1 κ monoclonal antibody that selectively inhibits IL-17A, is ongoing (NCT02594098).

The IL-23/IL-17-targeted clinical trials should reveal the potential of Th17/IL-23 antagonism in controlling atopic dermatitis, and special attention should be paid to ethnic or pediatric atopic dermatitis subpopulations with higher Th17 activation.

In contrast to IL-17A, which is produced by Th17 cells as well as in various innate immune cells, the main source for IL-17C appears to be epithelial cells, and it affects neighboring cells via autocrine manner, regulating innate epithelial immune pathways, with synergistic effects with IL-1 and IL-22 [91]. Furthermore, neutralization of IL-17C was shown to reduce skin Inflammation in murine models of atopic dermatitis, reinforcing the possible pathogenic role of IL-17C [91,92].

This assumption was examined in a phase I randomized, placebo-controlled clinical trial of MOR106 for atopic dermatitis, a fully human IgG1 κ monoclonal antibody selectively inhibiting IL-17C. This early-phase proof-of-concept trial showed promising clinical results and a good safety profile, and phase II clinical trials are expected [21].

OTHER THERAPEUTIC STRATEGIES

In addition to monoclonal antibodies developed for atopic dermatitis-specific cytokines, it is important to acknowledge some broader agents that will also potentially contribute to the expanding toolbox of atopic dermatitis drugs.

The Janus kinases (JAKs) are a family of tyrosine kinases, including JAK1, JAK2, JAK3, and TYK2. Phosphorylation of the intracellular domain of various cytokine receptors by JAKs results in binding and activation of the transducer and activator of transcription (STAT) [93–95]. The JAK-STAT signaling then mediates a range of intracellular immune dysregulations, including robust Th2 responses [96]. JAK inhibitors are small molecules that block intracellular signaling of the common γ_c receptor, shared by IL-2, IL-4, IL-9, IL-7, IL-15, and IL-21 [97,98]. The consequence is a potent, nonspecific, antagonism of various inflammatory axes.

Three different systemic JAK inhibitors are currently assessed in randomized, double-blind, placebo-controlled clinical trials for atopic dermatitis. Baricitinib, a JAK 1 and JAK 2 antagonist, had already demonstrated promising clinical efficacy in a phase II trial for atopic dermatitis [99], and is now in ongoing phase III trials (NCT03435081).

Upadacitinib, a JAK1 antagonist, showed great clinical efficacy so far in a phase II clinical trial, with

up to 50% of patients achieving EASI-90 in the drug-treated group [100] (NCT02925117). A third JAK inhibitor, PF-04965842, is another specific JAK1 inhibitor investigated for atopic dermatitis. PF-04965842 was also studied in a phase II clinical trial, and showed favorable, significant, clinical efficacy as compared with placebo [101] (NCT03349060).

Another class of oral small molecules, antagonizing histamine H₄ receptor (H₄R), may also be an optional therapeutic for atopic dermatitis in the future, as evidence suggests that histamine inhibits the terminal differentiation of keratinocytes and impairs skin barrier in atopic dermatitis, in addition to pruritus induction [102]. A phase II clinical trial of ZPL-3893787, an H₄R antagonist, is ongoing (NCT02424253). In addition, a novel class of orally available H₄R antagonists showing strong antiitching and antiinflammation activity in murine models may soon be tested in human clinical trials for atopic dermatitis [103].

CONCLUSION

Dermatology is moving towards targeted, narrow, efficacious, and well tolerated therapies, specifically antagonizing pathogenic immune components. atopic dermatitis is the next inflammatory skin disease to go down this path, as rigorous ongoing research refines the unique, complex, immune fingerprint of the disease, composed of diverse phenotypic subtypes, as atopic dermatitis varies among different subpopulations. This challenging mission is progressing as multiple ongoing clinical trials are evaluating monoclonal antibodies and new broad-acting agents for atopic dermatitis. These trials will not only result in a new, improved, clinical management of atopic dermatitis but will also help to dissect the contribution of the different immune axes and specific cytokines being treated, to the clinical phenotype of atopic dermatitis.

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