

REVIEW ARTICLE

Anti-inflammatory therapies in atopic dermatitis

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Abstract

The pathogenesis of atopic dermatitis (AD) is multifactorial and complex. Consequently, clinical signs and symptoms vary strongly depending on individually relevant trigger factors and the stage of the disease. So far, treatment of AD was commonly limited to topical treatment or, in more severe cases, to systemic drugs mostly approved for other indications than AD. However, emerging data on new anti-inflammatory agents have been published in the recent years. As these new substances specifically focus on immune responses in AD, these are partially considered as possible ‘breakthrough’ in the treatment of AD. Therapeutic strategies of the future appear to be ‘customized’ for inflammation in AD as they target pro-inflammatory, highly relevant cytokines and cytokine receptors, such as IL-4R α , IL-13, IL-31, and IL-17. Further innovative therapeutic approaches aim to block the function of relevant molecules such as thymic stromal lymphopoietin, chemoattractant-receptor homologous molecule expressed on Th2 lymphocytes (CRTh2), and phosphodiesterase (PDE)-4 inhibitors. Recently, anti-inflammatory effects in AD by antagonizing the histamine (H)-4 receptor have also been detected. Finally, specific immunotherapy is under further investigation as treatment option for AD patients with clinically relevant sensitization.

Atopic dermatitis (AD) is an inflammatory skin disease characterized by a chronic relapsing course and severe symptoms of itch (1). In the presence of a complex genetic predisposition (2), manifold adaptive immune responses to potential trigger factors such as food and inhalant allergens, microbial antigens, and self-antigens have been identified so far (3, 4). Pro-inflammatory immune responses in AD are mediated by both the humoral and the cellular immune system involving T cells, dendritic cells, mast cells, and keratinocytes (5). Signs and symptoms of AD vary strongly depending on the stage of the disease (6). So, due to a complex pathogenesis and the individual course of the disease (7), effective treatment with long-term improvement of skin inflammation still represents a challenge (8, 9).

Here, we provide an overview on emerging new findings in research on therapeutic agents and interventions which open promising perspectives on anti-inflammatory treatment in AD in future (Table 1).

Targeting cytokines and cytokine receptors

Anti-IL-4 receptor – a milestone in treatment of AD

IL-4 represents a classical Th2-type cytokine as it is responsible for the induction of Th2 polarization of naïve Th0

lymphocytes and, in turn, is secreted by Th2 cells, but also by basophils and natural killer T cells (10). In various studies, the pathophysiological relevance of IL-4 secretion for acute inflammation and, particularly, for allergen-specific immune response mechanisms in AD has been reported. For example, house dust mite-specific T lymphocytes have been demonstrated to secrete significant amounts of IL-4 in AD (11). A significant increase in serum levels of IL-4 could also be observed in grass-pollen-sensitized patients experiencing a significant flare-up of AD upon grass-pollen exposure (12). In addition, IL-4 secretion has recently been detected also for CD8⁺ T cells specific for the autoallergen α -NAC (13). It is well established that IL-4 promotes antibody isotype class switching to immunoglobulin E (IgE) (14) and acts as an inflammatory cytokine. As IL-4 induces a significantly reduced filaggrin expression (15, 16), it is also considered to substantially contribute to an impaired skin barrier function in AD. IL-4 binds to the IL-4 receptor as well as to the IL-13 receptor and, therefore, shares a variety of immunological functions with IL-13.

Based on this, therapeutic approaches resulting in a blockade of IL-4 functions have extensively been studied. Here, a fully human monoclonal, namely dupilumab, represents the most emerging new drug currently studied for the treatment

Table 1 Overview on current clinical trials on treatment of AD.

Target	Agent	Current status of clinical trial phase
IL-4R α	Dupilumab	Phase III
IL-13	Lebrikizumab	Phase II
	Tralokinumab	Phase II
IL-17	Secukinumab	Phase II
IL-22	ILV-094	Phase II
IL-31	CIM331	Phase II
	(Nemolizumab)	
IL-31R	BMS-981164	Phase I
IL-12/IL-23p40	Ustekinumab	Phase II
TSLP	Medi9929	Phase II
CRTh2	QAW039	Phase II
JAK inhibitor	Pf-04965842	Phase II
PDE-4 inhibitor	<i>Topical</i>	
	Cipamfylline	Phase II
	Crisaborole	Phase III
	E6005	Phase II
	<i>Oral</i>	
	Apremilast	Phase II
IgE-specific immunoadsorption	–	Phase II
CD20	Rituximab	–
Histamine-4 receptor	ZPL-389	Phase II
Specific immunotherapy in aeroallergen-sensitized atopic dermatitis patients	Extracts from different inhalant allergens	Phases II and III

JAK, Janus kinase; TSLP, thymic stromal lymphopoietin.

of AD (5). Dupilumab targets the IL-4 receptor alpha subunit (IL-4R α), which is shared by IL-4 and IL-13 receptors, and therefore antagonizes IL-4 and IL-13 signal transduction (17). In phase II studies, subcutaneous administration of dupilumab in patients with AD was highly effective leading to rapid improvement of both eczematous lesions and subjective symptoms (17–19). Furthermore, dupilumab shows a good safety profile: So far, nasopharyngitis has been reported as most frequent adverse event (19). Considering these promising data, approval of dupilumab for the indication of AD is eagerly expected. There are actually several phase III trials ongoing on long-term safety of dupilumab in children and adults with AD (20).

IL-13

IL-13 binds to the IL-13 receptor (i.e. IL-13R α 1 and IL-13R α 2) and also the IL-4 receptor (i.e. IL-4R α –IL-13R α 1). Therefore, its functions are in part congruent with those of IL-4 (5). IL-13 is predominantly secreted by CD4⁺ Th2 lymphocytes as well as by CD8⁺ cells (21) and substantially activates B cells with following differentiation and IgE synthesis. Comparison of the cytokine production of peripheral blood mononuclear cells of extrinsic AD and intrinsic AD patients and normal control individuals after stimulation

with anti-CD3 and/or anti-CD28 monoclonal antibodies revealed that in AD, signaling by the T-cell receptor complex with increased IL-13 secretion is largely independent of CD2 costimulatory signals (22). IL-13 plays a key role in cutaneous inflammation in the acute stage of AD, but is also discussed to contribute to the chronification of eczema (23). Beyond this, increased serum levels of IL-13 have been described as an immunological characteristic of an ‘allergic march-associated AD phenotype’ (24).

Treatment with monoclonal antibodies directed against IL-13, such as lebrikizumab and tralokinumab, in AD is currently being trialed in phase II studies (25, 26).

IL-17 – therapeutic option for intrinsic AD?

The majority of members of the IL-17 family, that is, IL-17A, IL-17F, and IL-17AF, are produced by Th17 cells, while IL-17E is secreted by Th2 cells (5). Next to T cells, mast cells have also been found to produce IL-17 (27). Effects of this cytokine are particularly relevant for inflammation in psoriasis. As a consequence, a monoclonal IgG1 antibody directed to IL-17A, secukinumab, has been approved for the indication of psoriasis vulgaris.

However, increased numbers of Th17 cells could also be detected in acute eczematous lesions and peripheral blood of patients with AD (28). Interestingly, this observation was made in Asian AD which has been characterized as a phenotype unifying features of psoriasis and AD (29). Furthermore, comparison of the molecular and cellular skin pathology between severe extrinsic and intrinsic AD revealed a higher activation of Th17 and Th22 cells and positive correlations between Th17-related molecules and SCORAD scores in patients with intrinsic AD (30). With regard to their functional relevance, ‘tissue remodeling’ properties have been identified for Th17 cells in AD (31).

Based on this, it might be supposed that treatment targeting IL-17 has beneficial effects particularly in patients with intrinsic AD. However, data from clinical trials are required for sufficient evaluation of possible risk and benefits of anti-IL-17 treatment in AD. There is actually one randomized, placebo-controlled phase II study investigating the effects of secukinumab in both extrinsic and intrinsic AD (32).

IL-22

IL-22 is a member of the IL-10 cytokine family. In AD, CD4⁺ T cells, namely Th17 and Th22 cells, and CD8⁺ T cells (21) as well as natural killer cells and mast cells (33) have been reported as sources for IL-22 production. Activated Th22 cells could be observed in the circulation of patients with AD and, moreover, increased numbers of skin-homing Th22 cells have been detected in inflamed skin lesions (34, 35). IL-22 binds to the IL-22 receptor 1 on keratinocytes. Its key functions comprise tissue repair as well as host defense mechanisms at the mucosa by stimulating epithelial cells (5, 36). It is further discussed that IL-22-producing Th22 lymphocytes are particularly relevant for transition to the chronic stage of AD (37). This hypothesis is

supported by previous findings from experimental studies that demonstrated an increased IL-22 secretion in skin-infiltrating CD4⁺CD45RO⁺CD45RA[−] memory T cells induced by staphylococcal exotoxin B (38). Similarly to Th17 cells, a higher activation in patients with intrinsic AD has also been reported for Th22 cells (30).

To date, no data on clinical experience with anti-IL-22 therapy in AD are available. There is actually one ongoing phase II study investigating the effects of intravenous application of an anti-IL-22 antibody (ILV-094) on clinical signs and symptoms of AD (39).

IL-31 – breaking the vicious circle

IL-31 represents a pro-inflammatory cytokine with multidimensional functions in the pathogenesis of AD (40–42):

Sonkoly et al. (43) reported significant overexpression of IL-31 in pruritic eczematous lesions and, moreover, serum levels of IL-31 in children with AD have been demonstrated to correlate significantly with the disease severity (44). Th2- and Th22 cells, but also mast cells, have been identified as source of IL-31 (27, 41). Thus, the detection of IL-31 and its functions further elucidated the complex pathogenesis of itch symptoms in inflamed skin in AD (45).

As IL-31 is induced by staphylococcal exotoxins (46), this cytokine is also supposed to be involved in *Staphylococcus aureus*-related skin inflammation. IL-31 acts as an inflammatory cytokine on keratinocytes (47). Moreover, data from a human organotypic skin model indicate that IL-31 has interfering effects on keratinocyte differentiation and the expression of filaggrin expression (48). So, IL-31 seems to contribute to an impairment of the skin barrier function in AD.

Considering the broad potential of pro-inflammatory effects of IL-31 in AD, therapeutic interventions antagonizing this cytokine or its receptor would be expected to reduce itch symptoms and acute skin inflammation and, finally, to contribute to a reconstitution of the skin barrier function. First promising data of a phase I/Ib clinical trial using a humanized anti-IL-31 receptor A monoclonal antibody (CIM331) have been published in 2016 (49). Here, patients received a single subcutaneous injection of the antibody. At week 4, a decrease in subjective symptoms (pruritus and sleeplessness) was observed while the substance was well tolerated (49). Meanwhile, a 12-week, double-blind, placebo-controlled, phase II trial on the efficacy and safety of different dose regimen of the same agent in AD has been performed (50). In this study, data analysis also revealed a significant improvement of pruritus in those patients who had received subcutaneous injections of CIM331 compared to placebo. The mean change in EASI score was 44.6% upon treatment with 0.5 mg/kg CIM331 (vs 20.9% in the placebo group) (50). In addition, injections of this monoclonal antibody were well tolerated.

A phase I study on the safety of an antibody targeting IL-31 (BMS-981164) has been completed, but corresponding data have not been published so far (51).

In summary, antagonizing IL-31 or IL-31R seems to be a promising treatment strategy. Further *in vitro* and clinical

research is necessary to assess the complete spectrum of immunological and clinical effects of anti-IL-31(R) therapy in AD.

IL-12/IL-23p40

The cytokines IL-12 and IL-23 have been described to stimulate macrophages, dendritic cells, natural killer cells, and activated T cells (36). Both these cytokines consist of the subunit p40. By targeting the IL-12/IL-23p40 subunit, the monoclonal IgG1 antibody ustekinumab antagonizes Th1, Th17, and Th22 activation. Treatment with this agent has been approved for the indication of psoriasis vulgaris.

Based on experiences in patients with psoriasis, Puya et al. (52) used ustekinumab for off-label treatment in a 21-year-old Caucasian patient suffering from severe refractory AD. Treatment doses were administered according to the psoriasis therapy regimen. Remarkably, pruritus already improved after 2 weeks and healing of eczematous lesions started 1 month after first dosing. Similar observations were made in another patient with extrinsic AD (53). Successful treatment with ustekinumab has recently been reported also for an adolescent patient with AD who had been treated with 45 mg ustekinumab per dose according to the psoriasis therapy regimen (54). By contrast, Samorano et al. (55) published clinical data from two patients with extrinsic AD where treatment with ustekinumab was not successful.

Robust data from randomized, controlled studies using ustekinumab in AD remain to be generated to have a representative overview on its possible therapeutic effects. To date, results from a first double-blind controlled study including 33 patients suffering from moderate-to-severe disease have been published (56): While ustekinumab was well tolerated, non-significant improvement of AD in the verum group (measured by SCORAD) was observed at weeks 12, 16, and 20. The authors further describe immunological findings with modulated Th1, Th17, Th22, and Th2 genes. As the use of mild topical glucocorticosteroids was allowed throughout the study, this condition is discussed as relevant interfering factor for the outcome of this study. Another phase II study has been completed in Japan, but corresponding data are not yet available (57).

Targeting molecules of special interest

Thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) has been identified as a relevant molecule for inflammatory immune processes particularly located at the epithelial interface. In the skin, TSLP is released by keratinocytes and Langerhans cells (58). In a mouse model, it was further demonstrated that via the TSLP receptor, which is expressed on antigen-specific T cells, TSLP leads to the secretion of Th2 cytokines and that Th2 polarization could, in turn, be blocked again by anti-TSLP (59). Beyond this, TSLP seems also to contribute to IL-17A production (60). Aside from these pro-inflammatory effects, TSLP seems also to play an important role for the induction

of itch. In an animal model, Wilson et al. (61) observed TSLP-mediated interaction between keratinocytes and cutaneous sensory neurons.

Considering this, TSLP is currently discussed as a relevant therapeutic target for the treatment of allergic diseases and AD (62). Indeed, several studies on effects of anti-TSLP therapy mainly in asthma have been initiated so far. With regard to AD, there is actually one ongoing phase II study (63). Results from randomized, placebo-controlled clinical trials will further elucidate the therapeutic potential of anti-TSLP treatment in AD.

Chemoattractant-receptor homologous molecule expressed on Th2 lymphocytes (CRTh2)

CRTh2 represents a prostaglandin receptor selectively expressed on Th2 cells (64). In AD, a preferential increase in CRTh2+ cells could be observed particularly within the disease-related cutaneous lymphocyte-associated antigen (CLA)-positive, but not within the CLA-negative, CD4+ lymphocyte compartment (64). By genotyping for polymorphisms in CRTh2, genetic variation of CRTh2 has been discovered that has an influence on the development of allergic diseases (65).

A series of CRTh2 antagonists has already been investigated for the treatment of allergic diseases in clinical studies (66–68). For the indication of AD, a phase II trial on effects of oral treatment with a CRTh2 antagonist in patients with moderate-to-severe disease has been completed (69), but the outcome of this study has not been published so far.

Janus kinase inhibitor

The JAK–STAT pathway plays a key role for Th2 polarization, activation of eosinophils, and B-cell differentiation and is activated by IL-4 (70).

As successful oral treatment with the Janus kinase (JAK) inhibitor tofacitinib citrate in a case of plaque psoriasis and alopecia totalis had previously been reported (71), its efficacy was further investigated in six consecutive patients with moderate-to-severe AD (72). Indeed, marked improvement upon this therapy could also be observed in AD with significant decrease in SCORAD index score in all patients during 8–29 weeks of treatment (72). Moreover, data on topical treatment with tofacitinib in adulthood AD have recently been reported: In a 4-week, double-blind, vehicle-controlled phase IIa study, 69 patients with moderate-to-severe AD were randomly allocated to a treatment group, who received 2% tofacitinib ointment twice daily, or to a control group. At week four, a significantly higher decrease in EASI score could be observed in the treatment group compared to the vehicle control group (73).

In conclusion, JAK inhibitors represent a further promising treatment option. Therapeutic effects remain to be further investigated in randomized, controlled trials. There is actually one phase II trial recruiting patients with AD for systemic treatment with the JAK inhibitor PF-04965842 (74).

Phosphodiesterase (PDE)-4 inhibitors

PDE-4 has been detected in T and B cells, macrophages, monocytes, neutrophils, and eosinophils (75). Twenty years ago, Hanifin et al. (76) demonstrated a reduced prostaglandin E2, IL-10, and IL-4 production in atopic mononuclear leukocyte cultures by selective high-potency PDE inhibitors.

With regard to topical treatment with PDE-4 inhibitors in clinical trials, beneficial therapeutic effects of ciprofylline cream in AD were less compared to a moderately potent topical steroid (77). By contrast, first data on a new compound, namely crisaborole, are promising: Recently, in two phase III studies ‘Investigator’s Static Global Assessment’ success was observed in a higher proportion of patients applying crisaborole compared to the vehicle-treated group (78). Additionally, an earlier decrease in pruritus was observed upon verum treatment compared to the vehicle control (78). In a Japanese study, the safety and efficacy of topical application of another PDE-4 inhibitor, E6005, over a period of 4 weeks in adulthood AD have been investigated (79). This agent was well tolerated and, furthermore, first clinical assessments also reflect trends toward improvement of AD with significant reduction in EASI score and objective SCORAD and SCORAD-C (79). Further investigation of the efficacy of different concentrations of E6005 for topical localized, short-term treatment in AD revealed concentration-dependent effects with a significant reduction in severity scores by treatment with 0.2% E6005 ointment (80).

In addition to topical treatment, systemic therapy with PDE-4 inhibitors has been investigated. Apremilast represents a PDE-4 inhibitor with approval for the indication of moderate-to-severe plaque psoriasis and active psoriasis arthritis. Meanwhile, therapeutic effects of apremilast have also been investigated for AD. In an open-label study including 16 patients with AD, dosing of 20 mg apremilast daily over 3 months was described to significantly reduce pruritus and to improve quality of life, while a dose of 30 mg apremilast daily led to a significant reduction in EASI score (81). In a similar study, 10% of subjects receiving 20 mg apremilast daily reached EASI-75 and another 10% EASI-50 (82). Apremilast was well tolerated in both studies. Moreover, data have been published on beneficial effects of apremilast in an 8-year-old patient with refractory AD (83). In this case report, the patient had already received systemic therapy with glucocorticosteroids, extensive topical anti-inflammatory treatment, and omalizumab for asthma. Due to persisting high disease activity, off-label treatment with apremilast 30 mg once daily was started 5 months later (83). The authors observed rapid improvement of pruritus by 2 weeks of treatment followed by a reduction in inflammation and excoriation of the skin lesions.

Overall, for comprehensively evaluating the therapeutic potential of PDE-4 inhibitors in AD, randomized, placebo-controlled trials remain to be initiated. To date, one randomized, placebo-controlled phase II multicenter study on the efficacy of apremilast in AD has been completed, but the data are not available yet (84).

Targeting B cells and IgE antibodies

In the skin and blood of patients with AD, significantly increased numbers of cluster of differentiation (CD) 19+CD20+ B cells can be observed (85). Additionally, the vast majority of patients with AD show elevated total and/or specific IgE levels. Consequently, B cells and IgE antibodies have both been investigated as further targets for anti-inflammatory treatment strategies in AD.

While the humanized, monoclonal anti-IgE antibody omalizumab is approved for the treatment of severe bronchial asthma, case series and controlled studies with patients with AD revealed beneficial effects of this agent only in individual cases (86–88). Based on this, omalizumab cannot actually be recommended for treatment of AD (89, 90). However, first data support the hypothesis that there is a subgroup of patients with AD that might respond to treatment with omalizumab. These patients are supposed to be characterized by the absence of filaggrin mutations and a distinct lipid metabolite profile (91).

As further therapeutic approach in targeting IgE antibodies, *ex vivo* immunoadsorption has been investigated. In an open-label pilot study, 12 severely diseased adults with total IgE levels >4500 IU/l were included (91). The patients underwent a total of 10 immunoadsorptions within 5 weeks using polyclonal sheep antihuman immunoglobulin antibodies. By week 3, a significant reduction in the mean SCORAD occurred which could still be observed at week 13 (59% reduction) (92). In a further pilot study in this field, extracorporeal immunoadsorption was combined with omalizumab treatment in 10 patients (93). During and 6 months after treatment, IgE levels continuously decreased in all patients. Concomitantly, AD symptoms improved during the treatment phase, but a relapse was observed after the end of treatment (93).

Rituximab represents a chimeric monoclonal antibody binding to CD20 which is expressed on immature and mature B cells (94). This agent has been approved for several indications in hemato-oncology and rheumatology.

In a pilot study including six patients with AD, two intravenous doses of 1 g rituximab at an interval of 14 days led to a significant decrease in EASI score within 4–8 weeks (95). In a further case report, a woman suffering from recalcitrant AD experienced marked improvement of the disease severity after having received rituximab once (96). By contrast, Sediva et al. (97) presented two cases of severe AD where long-term improvement of AD could not be achieved by treatment with rituximab. In both these cases, two doses (at an interval of 14 days) of only 500 mg rituximab were administered.

Taken together, data from (further) randomized, placebo-controlled trials on the safety and beneficial effects of immunoadsorption as well as rituximab in AD are lacking. Treatment of AD with IgE-specific immunoadsorption is currently investigated in a phase II study (98). Notably, rituximab is currently not under investigation for the indication of AD in clinical trials.

Histamine-4 receptor – a new target for anti-inflammatory therapy

Severe itch represents a key symptom of AD: Dry or, particularly, inflamed skin accompanied by itch symptoms provokes scratching which, in turn, further contributes to perpetuation of skin inflammation.

Neuropeptides, pro-inflammatory cytokines such as IL-31, TSLP and, classically, histamine have been identified as relevant mediators of this phenomenon which has been termed 'itch-scratch-circle' (45, 99).

While in patients with chronic urticaria, oral therapy with antihistamines targeting the histamine (H)-1 receptor represents the first step of a multistep therapy regimen (100), there is no evidence for beneficial therapeutic effects of H1 antagonists in AD. According to the current guideline on treatment in AD, H1 antihistamines should only be used in combination with other treatments for individual, severe cases of adulthood AD (89, 90). Notably, in infants and adolescents the Commission on Drug Safety in Children of the German Society of Pediatrics and Adolescent Medicine advises against the use of sedating over-the-counter antihistamines as these carry the risk for a series of relevant side-effects such as paradoxical and neurotoxic reactions (89).

As a result, research in this field focuses more and more on the relevance of other histamine receptors of which the H4 receptor seems to play an important role in AD. Expression of H4 receptors was detected on Th2 cells, Th17 cells, keratinocytes and, moreover, sensory neurons (101–103) (Fig. 1). Remarkably, antipruritic, but also anti-inflammatory, effects could be observed by antagonizing the H4 receptor (104, 105). In a clinical phase IIa trial, the effects of the H4 receptor antagonist JNJ-39758979 *vs* placebo in AD were investigated over a period of 6 weeks (106). As two patients developed severe neutropenia, the study had to be discontinued prematurely. Despite low patient numbers, data analysis revealed significant dose-dependent effects on pruritus and (nonsignificant) improvement of eczema in verum-treated patients (106). In a further randomized, placebo-controlled phase IIa study, the selective H4 receptor antagonist, ZPL-3893787, was administered orally over 8 weeks to patients with moderate-to-severe AD (107). Above all, this agent was well tolerated. Remarkably, after treatment a 50% reduction in eczema area and severity index (EASI) score (*vs* 27% in the placebo group) and 41% reduction in SCORAD index score (*vs* 26% in the placebo group) occurred, while there were no significant differences in improvement of worst itch symptoms during the last 8 h between the two groups. The excoriation score extracted from the EASI score and the pruritus score extracted from the SCORAD score revealed, however, significant differences between the study and the placebo group (107). Based on this, it could be concluded that this H4 receptor antagonist particularly has anti-inflammatory properties that are effective in AD.

Taken together, the H4 receptor represents a new target for anti-inflammatory treatment strategies in AD. Further clinical and experimental studies on selective H4 receptor

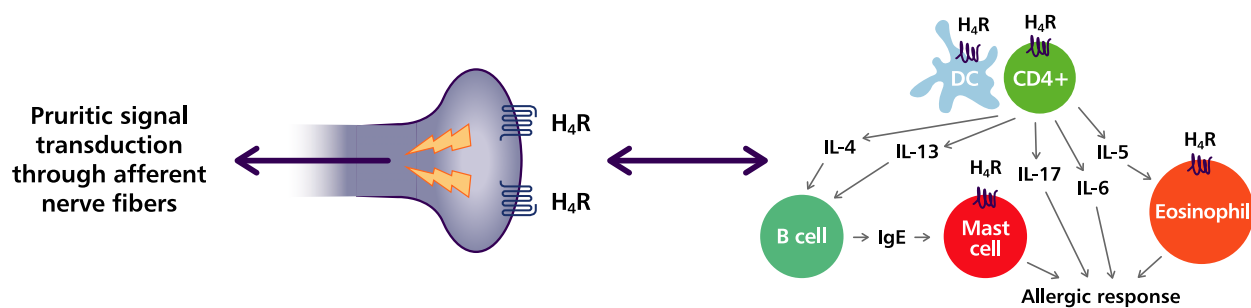


Figure 1 The histamine (H)-4 receptor is expressed on sensory neurons as well as on CD4+ T cells and dendritic cells (kindly provided by Steve Liu, Ziarno Pharma Ltd).

antagonists such as ZPL-389 are needed to better define related therapeutic effects in AD, the risk/benefit ratio and, finally, characteristics of patients with AD who may particularly benefit from treatment with H4 receptor antagonists.

Targeting allergen-specific immune response mechanisms

Specific immunotherapy

Eighty percent of adult patients with AD are characterized by specific IgE sensitization to seasonal and/or perennial allergens. A seasonal flare-up has been reported for a subgroup of sensitized patients supporting the relevance of inhalant sensitization in these patients (108, 109). Indeed, in a recent randomized, placebo-controlled, double-blind proof-of-concept study, significant worsening of eczema upon grass-pollen exposure in grass-pollen IgE-sensitized AD patients could be observed (12). Moreover, late-type reactions to food in a subgroup of sensitized children and adults with AD could be verified (109). In conclusion, there is increasing evidence for the relevance of allergen-specific sensitization for signs and symptoms of AD in a subgroup of patients (110–113).

For these patients, specific immunotherapy (SIT), unlike pharmacotherapy, represents an efficient causal treatment option. Since the last century, this approach has been investigated for AD. Despite promising data from randomized, controlled trials in this field (114, 115), the overall evidence on

beneficial effects of SIT in AD is currently not sufficient as has been stated in a systematic Cochrane review this year (116). Notably, from their systematic data analysis the authors further conclude that SIT in AD is not accompanied by an increased risk for local or systemic adverse events (116).

According to the current recommendations on treatment in AD, SIT can be recommended in patients with AD for the indication of allergic airway diseases (89). For the indication of AD, SIT can be considered in patients who suffer from severe AD suspected to be substantially triggered by inhalant allergens (89).

As *in vitro* data indicate that the phenotype of allergen-specific T cells differs between allergic airway diseases and AD (11), further studies in this field are necessary. The next step in optimizing SIT in AD could be a modified composition of allergen extracts. These should be adapted to disease-specific immunological features present in AD. For this purpose, further data from T-cell epitope mapping of relevant allergens using peripheral blood from patients with AD remain to be generated.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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