



Current novel approaches in systemic therapy of atopic dermatitis: specific inhibition of cutaneous Th2 polarized inflammation and itch

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Purpose of review

This present review gives an overview on different approaches on systemic treatment of atopic dermatitis with a focus on molecules that are presently investigated as defined target structures in clinical studies with patients with atopic dermatitis.

Recent findings

Available systemic drugs for the treatment of atopic dermatitis are limited. There is a high need for the development of new treatment regimen. Current studies address novel biologicals or small molecules for the treatment of atopic dermatitis. In particular, interventions in the T-helper 2 cell (Th2) allergic inflammation are promising. Dupilumab, a humanized monoclonal antibody to the interleukin-4R is the first antibody (i.e. 'biological') with published efficacy shown in controlled prospective studies in atopic dermatitis. A number of other target molecules is currently addressed in clinical studies with blocking antibodies against target molecules of Th2 polarized inflammation in atopic dermatitis (e.g. interleukins 13, 22, 31, thymic stromal lymphopoietin). Inhibiting phosphodiesterase-4, chemoattractant receptor-homologous molecule 2, the histamine-4 receptor, or the neurokinin-1 receptor may lead to the approval of novel 'small drugs' for a specific treatment of atopic dermatitis. Antifungals may be helpful in the variant of head and neck dermatitis associated with sensitizations against *Malassezia* species. Induction of specific immune tolerance (e.g. with allergen-specific immunotherapy) should be further studied in terms of the management of atopic dermatitis because available clinical studies resulted in inconsistent results on the skin condition.

Summary

Current studies with new substances for the systemic treatment of atopic dermatitis have tremendous implications for the future management of atopic dermatitis.

Keywords

atopic dermatitis, clinical studies, dupilumab, histamine-4-receptor, systemic treatment

INTRODUCTION

Atopic dermatitis is the most common skin disease in childhood and shows a chronic course with a prevalence of 1–2% in adolescence and adulthood [1]. Atopic dermatitis shares general features of barrier dysfunction and skin inflammation with other inflammatory diseases of the skin, such as psoriasis or allergic contact dermatitis. Disease factors have been identified in atopic dermatitis as well and current treatment concepts take immune dysregulation both of the adaptive and the innate immune system into account [2,3,4]. Systemic treatment of atopic dermatitis is needed if the patient does not respond sufficiently to basic and anti-inflammatory topical treatment. Of systemic immunosuppressive treatments, efficacy has been shown with

azathioprine, ciclosporin, methotrexate, and mycophenolate mofetil. The overall treatment benefit is at least 50% improvement in clinical signs measured with eczema scores, such as Eczema Area and Severity Index (EASI) or SCORAD or pruritus scores [5,6]. A high need exists for the development of drugs

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KEY POINTS

- The arsenal of available systemic drugs for the treatment of atopic dermatitis is limited.
- No drugs are approved for the treatment of children with atopic dermatitis and in adults only broadly acting immunosuppressant drugs are available for treatment, most of them off label.
- In consequence, there is a high need for the development of novel more specific treatment regimen.
- Ongoing interventions in the Th2 allergic inflammation, for example, with anti-IL-4R, anti-IL-13, IL-31, or anti-TSLP antibodies or with histamine-4, PDE4, or CRTH2 inhibitors are highly promising.
- First studies with the anti-IL-4R antibody dupilumab resulted in beneficial effects on atopic dermatitis.

interfering with more disease specific mechanisms in atopic dermatitis.

The current review focuses on recent publications on systemic treatment in atopic dermatitis. Previous studies may be covered in more detail in other review articles [1,5[■],6]. More detailed information on ongoing clinical studies in atopic dermatitis is found at <https://clinicaltrials.gov/> and in further reviews [7[■],8[■],9[■]].

Target structures for available biologicals with limited effects on atopic dermatitis

A number of publications describe off label applications of available biologicals for atopic dermatitis (Table 1) [8[■],9[■],10]. Targeting the molecules of the following immunological relevant molecules had

only low effects on the skin condition or on pruritus in atopic dermatitis.

Tumor necrosis factor α

Tumor necrosis factor α (TNF α) inhibitors (etanercept, adalimumab, infliximab) are approved for the treatment of psoriasis and some internal diseases. Antagonists against TNF α have also been studied in a limited number of patients with atopic dermatitis with rather disappointing results. Only two of nine patients with atopic dermatitis showed long-term improvement upon treatment with the TNF α antibody infliximab [11] and two more patients did not respond to the TNF α blocker etanercept [9[■]]. Some reports even described a development of atopic dermatitis in some individuals [12,13], which indicates that TNF α – established target for the treatment of psoriasis – is not an adequate target molecule in the management of atopic dermatitis.

Immunoglobulin E

Although 80% of all patients with atopic dermatitis show elevated serum levels of total immunoglobulin E (IgE) and specific sensitization to food and inhalant allergens, treatment with the anti-IgE antibody omalizumab – approved for the treatment of severe asthma bronchiale and chronic urticarial – showed inconsistent results published in some case series. A randomized, placebo-controlled, double-blind investigation with omalizumab was conducted in 20 patients with severe atopic dermatitis. No effect on the severity of dermatitis was shown in this small study [14], although IgE and other immune parameters were significantly reduced. Interestingly, in a recent study [15[■]] severely affected patients

Table 1. Biologicals in atopic dermatitis [8[■],9[■],10]

Available biologicals with low or weak effect on atopic dermatitis	Anti-IgE (Omalizumab)
	Anti-IL-5 (Mepolizumab)
	TNF-inhibitors (Etanercept, adalimumab, infliximab)
Available biologicals with effects in open trials/case series	Anti-IL-6R (Tocilizumab)
	Anti-CD20 (Rituximab)
	Anti-IL-12/23 (Ustekinumab)
Biologicals in ongoing clinical studies	Anti-IL-4R (Dupilumab)
	Anti-IL-12/23 (Ustekinumab)
	Anti-IL-13 (Tralokinumab, Lebrikizumab))
	Anti-IL-22 (ILV-094)
	Anti-IL-31 (BMS-981164)
	Anti-IL-31R (CIM331)
	Anti-TSLP (MK-8226, AMG 157)

without mutations in filaggrin mutation responded to omalizumab, whereas those who showed filaggrin mutations (and a skin barrier defect) did not. These suggest that anti-IgE may have a moderate effect on cutaneous atopic (allergic) inflammation if this is not amplified by inherited skin barrier defects.

Interleukin-5

Interleukin-5 (IL-5) is a key cytokine for eosinophilic differentiation and activation and is elevated in lesional skin and in the blood of patients with atopic dermatitis. Mepolizumab, a humanized monoclonal antibody targeting IL-5, did not significantly reduce skin disease severity in patients with atopic dermatitis, although it reduced eosinophils in the circulation in a small placebo-controlled study [16] performed some years ago. As trends of improvement were observed in this short-term study applying only two infusions of anti-IL-5 antibody or placebo, it may be possible that longer treatments may be needed to achieve treatment success atopic dermatitis.

Target molecules for available biologicals with beneficial effects on atopic dermatitis in open trials/case series

Three available antibodies approved for the treatment of other diseases have been published to be potentially effective also on the skin condition in atopic dermatitis. One of them (ustekinumab) is therefore evaluated in controlled clinical studies.

Interleukin-6

IL-6 is a pleiotropic and strong proinflammatory cytokine produced under inflammatory conditions in the skin. Tocilizumab is an IL-6 receptor antibody approved for the treatment of rheumatoid arthritis. Application of the antibody led to a greater than 50% reduction in the inflammatory score in three severely affected patients with atopic dermatitis. Unfortunately, two patients developed bacterial infections that suggests a limited usefulness in atopic dermatitis [17].

Anti-CD20 (B-lymphocytes)

Only low numbers of B-lymphocytes are detectable in the skin in atopic dermatitis. Nevertheless, CD20⁺ cells play a role in the regulation of adaptive responses and in the production of antibodies including IgE and may be targets for effective treatment of atopic dermatitis. Depletion of B-lymphocytes with rituximab led to significant

improvement in the skin condition in six individuals with moderate atopic dermatitis [18] but two patients with severe atopic dermatitis treated with rituximab did not show a significant reduction in skin disease severity [19]. The combination of omalizumab and rituximab was effective in four out of six patients with severe refractory atopic dermatitis [20], indicating a need for further studies until any conclusion can be drawn on the efficacy of the antibody in atopic dermatitis.

Interleukin-12 and interleukin-23

IL-12 and IL-23 are produced by dendritic cells and are elevated in lesional skin in atopic dermatitis compared with healthy controls. Both cytokines share a common protein chain (p40). IL-12 is considered to be proinflammatory in lesional skin strengthening TH1 polarized cytokine responses in the chronic phase of the disease whereas IL-23 may contribute to the upregulation of IL-17, which has been described rather in the acute phase of atopic dermatitis [21] and in allergic contact dermatitis [22]. Ustekinumab, approved for the treatment of psoriasis and psoriasis arthritis, binds to the common p40 subunit of IL-12/IL-23. Application of ustekinumab led to improvement of atopic dermatitis in patients with severe disease communicated in some case histories [23–25]. Trials evaluating ustekinumab in patients with moderate-to-severe atopic dermatitis are ongoing in Japan and United States.

Target structures for new biologicals in ongoing clinical studies on atopic dermatitis

The deeper understanding of the immunology and the inflammatory response in atopic dermatitis led to the initiation of a number of clinical trials with novel monoclonal antibodies in atopic dermatitis. Some of these antibodies had already been studied before allergic asthma bronchiale [26].

Anti-IL-4 receptor

The key T-helper 2 cell (Th2) cytokines of IL-4 and IL-13 share the α -chain of their receptors, which is critically involved in signal transduction into target cells of the cytokines. Dupilumab prevents IL-4/13 interactions with the α -subunit of the IL-4 receptor complex. In previous studies, dupilumab showed efficacy in patients with asthma and elevated eosinophils. Beck *et al.* [27^{••}] published four phase II studies with dupilumab in 2014 in one paper: The effect of the antibody was evaluated as

monotherapy in two 4-week trials and in one 12-week trial and in combination with topical glucocorticoids in another 4-week study. In all studies randomized, double-blind, placebo-controlled trials with adults who suffered from moderate-to-severe atopic dermatitis had been performed. Treatment with dupilumab resulted in dose-dependent improvements in clinical scores, pruritus, and biomarker levels. In the different studies at least 85% of patients in the dupilumab group, as compared with 35% of those in the placebo group, had a 50% reduction in the EASI score; reductions of pruritus scores were observed at the same time. When the substance was applied in combination with topical corticosteroids, all patients showed a reduction of the EASI score of at least 50%.

Independently, a transcriptomic analyses of pretreatment and posttreatment skin biopsy specimens from patients with moderate-to-severe atopic dermatitis who had been treated weekly with 150 or 300 mg of dupilumab or placebo was published [28[•]]. Dupilumab improved the inflammatory signature of atopic dermatitis in a dose-dependent manner and the molecular changes paralleled improvements in clinical scores. Significant decreases in mRNA expression of genes Th2-associated chemokines (CCL17, CCL18, CCL22, and CCL26) were noted without significant modulation of TH1-associated genes. This is of interest, as analyses in preclinical models of atopic dermatitis demonstrated chronicity of atopic dermatitis to also depend on IL-4 signaling [29]. Moreover, genes related to hyperplasia (K16 and MKI67) and to activated dendritic cells decreased following dupilumab as well.

Interleukin-13

IL-13 is considered to be a key Th2 cytokine with numerous effects in allergic reactions. Studies on treatment of refractory allergic asthma bronchiale with anti-IL-13 antibodies resulted in significant improvements of the disease [26]. In consequence anti-IL-13 antibodies (tralokinumab, lebrikizumab) are currently studied in atopic dermatitis as well.

Interleukin-22

The T-cell cytokine IL-22 is mainly produced by T lymphocytes and in inflamed skin also by mast cells [20–32]. It belongs to the IL-10 family of cytokines and induces activation of keratinocytes, which leads to the upregulation of inflammatory mediators in the epidermis and increased epidermal thickening. A pilot study with an anti-IL-22 antibody is presently ongoing.

Thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is a cytokine of the interleukin-7 family mainly produced and secreted by keratinocytes. The cytokine is upregulated in the skin of atopic dermatitis. The initially primary observed effect of TSLP was a polarization of dendritic cells toward Th2, involving the upregulation of the Th2-associated membrane molecule OX40 [33]. Later, the induction of pruritus was described in animal models [34,35]. The blockade of TSLP or its receptor appears, therefore, highly attractive for the treatment of atopic dermatitis, which is now studied in early clinical studies [8^{••},35].

Interleukin-31 and its receptor

IL-31 is a cytokine produced by Th2 cell, mast cells, and keratinocytes. The expression of IL-31 is elevated in atopic dermatitis skin and serum levels of IL-31 correlate with disease severity in patients with atopic dermatitis [36,37]. IL-31 works as a strong inflammatory cytokine on various cells expressing the IL-31 receptor. In addition, in mouse models IL-31 induced atopic dermatitis-like lesions and pruritus [37,38]. Therefore, the cytokine or its receptor are promising targets for the reduction of cutaneous inflammation and itch. Antibodies blocking IL-31 (BMS-981164) or its receptor (CIM331) are in ongoing clinical studies with patients with AD.

Novel target structures for small molecules in clinical studies on atopic dermatitis

In addition, biologicals and the available immunosuppressants some approaches targeting defined molecules with small molecules have been described or are currently under investigation for the treatment of atopic dermatitis (Table 2).

Histamine-4 receptor

Histamine binds to three different receptors in men. Inhibition of the histamine-1 receptors is not efficient in the reduction of dermatitis or pruritus in atopic dermatitis. Preclinical findings in mouse models and in-vitro studies with primary human cells suggest that inflammatory, Th2 polarizing and pruritic effects are mediated via the histamine-4 receptor. In clinical trials with humans, an antipruritic effect of histamine-4 receptor antagonists has been shown in histamine-induced pruritus-induced itch [39^{••},40].

Japanese patients with atopic dermatitis were randomly assigned to the histamine 4 antagonist JNJ-39758979 or placebo once daily for 6 weeks in a

Table 2. Small molecules for the treatment in atopic dermatitis [8[■],9[■],10]

Available drugs	Systemic glucocorticosteroids ^a
	Cyclosporin A ^b
	Azathioprin ^c
	Mycophenolatmofetil, Mycophenolic acid ^c
	Methotrexat ^c
Target molecules of small molecules in current clinical studies	Histamine 4 receptor (H-4R)
	Chemoattractant receptor-homologous molecule 2 (CRTH2 inhibitors)
	Phosphodiesterase-4 (PDE-4) inhibitors
	Neurokinine-1 receptor (NK1-R) antagonist
	Vitamin D receptor

^aOnly short-term usage recommended in atopic dermatitis.

^bApproved in many countries for adults with atopic dermatitis.

^cAvailable for off label use only in atopic dermatitis.

phase 2a, double-blind, multicenter, placebo-controlled study [41[■]]. A total of 88 of 105 planned patients were randomized before the study was stopped and unblinded for safety reasons. Although the study did not reach the primary end point (significant improvement of eczema after 6 weeks measured by EASI), improvements (i.e. decreases) in median EASI were observed with the histamine-4 receptor antagonist at week 6. In addition, pruritus significantly declined at that time in the small group of patients available for evaluation. Unfortunately, two patients developed serious neutropenia leading to premature study discontinuation. This side-effect is discussed to be caused by a metabolite of JNJ-39758979 and at least two novel histamine-4 receptor antagonists are meanwhile in further clinical studies.

Neurokinine-1 receptor

Substance P is a neurokinine released by the terminals of specific sensory nerves and is widely disturbed within the body. The severity of atopic dermatitis correlates with increased plasma levels of substance P, which may suggest efficacy of NK-1 receptor (NK-1R) antagonists in these patients [42]. Substance P acts via the NK-1R. In mouse models, substance-P induced was inhabitable by NK-1R antagonists. In humans, the NK-1R aprepitant was successfully applied in humans to reduce severe itch [10]. In atopic dermatitis, a phase II trial is performed to study the effect of this NK-1R antagonist on pruritus.

Phosphodiesterase-4

Studies starting already in the 1980s of the last century have shown that leukocytes from patients with atopic dermatitis have an increased phosphodiesterase activity compared with normal controls

contributing to inflammation [38]. Apremilast is an oral phosphodiesterase-4 inhibitor, which has been approved in 2015 for the treatment of psoriasis in many countries because of its efficacy in this disease. Apremilast also resulted in significant improvement of the skin condition in atopic dermatitis, that is reduction of dermatitis in 16 patients with atopic dermatitis [43]. Reduction of eczema by apremilast was confirmed in a second trial with 10 patients with atopic or allergic contact dermatitis [44]. A recent review compares clinical efficacy in atopic dermatitis to that of psoriasis [45].

Chemoattractant receptor-homologous molecule 2

Chemoattractant receptor-homologous molecule 2 (CRTH2) is expressed on Th2 cells eosinophils and basophils. The receptor mediates the activation and chemotaxis of these cell types in response to prostaglandin D2 (PGD2), produced and released by mast cells. The blockade of CRTH2 fits into the concept of Th2 antagonizing therapy regimen. A number of small molecules antagonizing CRTH2 are available and some of them have been shown to be effective in allergic asthma bronchiale [46,47]. The CRTH2 inhibitor OC459 is under study for the treatment of moderate-to-severe atopic dermatitis [20].

Vitamin D receptor

In a recently published study [48[■]], the effect of oral vitamin D on atopic dermatitis was investigated in Ulaanbaatar, Mongolia, in a population likely to have vitamin D deficiency in winter. The authors performed a randomized, double-blind, placebo-controlled trial of 107 children with atopic dermatitis worsening in winter between 2 months and

1 year. Compared with placebo, vitamin D supplementation for 1 month produced a clinically and statistically significant improvement in EASI score compared with placebo. In contrast, negative data had been published before from a cohort study [49] of 30 adults with atopic dermatitis in the USA. Although the mean serum 25OHD increased in the treatment group in that study, no significant change in EASI scores was observed. This suggests that vitamin supplementation for the treatment of atopic dermatitis may be an attractive approach in further studies on atopic dermatitis rather in populations with a higher probability of basic vitamin D deficiency.

Malassezia species

Malassezia species are thought to be involved in the variant of chronic head and neck dermatitis of atopic dermatitis in adulthoods. A recent investigation of 173 patients with atopic dermatitis showed that 50% had an IgE-mediated sensitization against Malassezia species. Patients with head and neck dermatitis had higher serum levels of specific IgE [50]. Previous controlled studies with the antifungal ketoconazole showed positive effect on atopic dermatitis in these patients. Recent retrospective analyses of 24 patients described beneficial effects on the skin condition in 17 patients treated with itraconazole. The duration of the mean application was 8 months [51].

Allergens addressed by specific immunotherapy with allergens

Studies on specific immunotherapy for the treatment of atopic dermatitis were reviewed in detail 3 years ago in this journal [52]. Briefly after this review one larger multicenter study applying specific immunotherapy in atopic dermatitis was published. Here, subcutaneous injections of a house dust mite extract were performed in sensitized adult patients. The primary end point (reduction of the eczema score in the treatment group compared with the placebo group) was not reached. However, subgroup analyses of highly affected patients revealed a significant and moderate beneficial effect of specific immunotherapy with mites on atopic dermatitis [53]. No larger cohort studies have been published since 2012 [54].

CONCLUSION

A number of new systemic treatment approaches are currently being studied in atopic dermatitis. First published results with a directed therapy inhibiting

Th2 cytokines, which signal through the IL-4 receptor are very promising. Efficient novel substances for the systemic treatment of atopic dermatitis are highly needed for a better management of this chronic and sometimes severe skin disease. They will have tremendous implications for the future management of atopic dermatitis.

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