What’s new in atopic eczema?

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Importance of the field: Atopic eczema (AE) is a chronic relapsing inflammatory skin condition and one of the most common, potentially debilitating diseases with increasing incidence.

Areas covered in this review: The complex etiology of AE with multiple systemic and local immunologic and inflammatory responses and interactions between susceptibility genes and environmental factors leading to defects in skin barrier function and eczematous skin lesions is presented. Knowledge of pathogenesis is important for understanding the more innovative treatment approaches discussed.

What the reader will gain: Basic therapy consists of hydrating topical treatment and avoidance of specific and unspecific provocation factors. For acute eczematous skin lesions, anti-inflammatory treatment consists mainly of topical glucocorticoids and topical calcineurin inhibitors (tacrolimus and pimecrolimus). Microbial colonization and superinfection may induce skin exacerbation, which can be treated by either topical or systemic antimicrobial treatment. Systemic anti-inflammatory therapy is limited to severe cases and consists of systemic steroids, cyclosporine A or mycophenolate mofetil. Novel anti-inflammatory concepts that go beyond corticosteroids are in the early phases of development. There are targeted therapeutic approaches, such as cytokine and chemokine modulators and it remains to be investigated how effective they will be and what side effects they may carry.

Take home message: Existing treatment modalities such as barrier repair therapy, topical immunosuppressive agents, antiseptic treatment as well as systemic treatment options are discussed. The review aims to summarize the most recent findings of more innovative treatment approaches such as modulation of cytokines or chemokines, modulation of T-cell responses or anti-IgE therapy.

Keywords: anti-inflammatory treatment, atopic eczema, biologicals, calcineurin inhibitors glucocorticosteroids, systemic therapy, topical therapy

1. Background

Atopic eczema (AE), also called atopic dermatitis, is a chronic, pruritic skin disease with a broad spectrum of clinical manifestations which affects up to 20% of children and 1 – 3% of adults in most countries of the world [1,2]. About 40 million patients suffer from AE and this inflammatory skin disease is often the first step in the so-called ‘atopic march’ that results in asthma and allergic rhinitis [2]. The ‘atopic march’ or ‘allergic march’ [2] is a term used for a typical sequence of clinical symptoms persisting for years. AE occurs first, followed by the development of asthma and allergic rhinitis in later life.

As a result of the increasing prevalence of atopic disorders in developed countries, the burden of healthcare cost increases and the quality of life of affected patients is significantly lowered by chronic eczematous lesions, pruritus, sleep loss, dietary restrictions and psychosocial affections.
Though the prevalence of atopic diseases rapidly increased over the last half century, AE and other atopic diseases have already been described in ancient China [3] and – according to Suetonius – emperor Augustus was suffering from ‘extremely itchy skin, seasonal rhinitis and tightness of the chest’ (Suetonius: De Vita Caesarum; [3]). The peculiar, antique, instrument-based scratching behavior (frequent use of a scraper) was one of Octavian’s atopy defining, eczema-specific habits.

The term ‘atopy’ was first defined by the allergists Coca and Cooke in 1923 as a proclivity to develop rhinitis, asthma and urticaria. They found that these patients possessed a distinct antibody, which they termed ‘reagin’ or ‘skin-sensitizing antibody’, after intradermal tests to a variety of inhalant allergens elicited urticarial lesions. In the early 1930s, Sulzberger encountered atopic patients with eczematous lesions that favored the antecubital and popliteal fossae and initially called the disease ‘neurodermatitis of atopic type’, later ‘atopic eczema’ and ‘atopic dermatitis’ [4].

Today, the terminology is still a subject of ongoing controversy and different synonyms are used for the disorder: ‘neurodermatitis’, ‘endogenous eczema’, ‘neurodermitis constitutionalis sive atopica’, ‘prurigo besnier’ and more; the heterogeneity of the terms used reflects the different concepts of pathophysiology.

One major feature of AE is the occurrence of eczematous lesions. The term ‘eczema’ is derived from the Greek word ‘ekzein’, that is, ‘to boil out’, which refers to the skin lesions flaring up (‘boiling out’) in a relapsing course. Nowadays, the terms ‘dermatitis’ and ‘eczema’ are regarded as synonymous. The term ‘atopic’ refers to the frequent association with atopy and the need to separate this skin disease from other forms of eczema, such as seborrhoeic, allergic contact, primary irritant, photo-allergic, phototoxic, nummular, asthmatic, stasis, dyschidrotic and drug-induced eczema. These other forms of eczema have other causes and distinct patterns.

The clinical definition of AE includes a typically age-related distribution and morphology [5]. Hanifin and Rajka stated the necessity of three of four main criteria (pruritus, typical morphology and distribution, chronic or chronically relapsing course and atopic personal or family history) in addition to three minor criteria among a list of 21. Various further attempts have been made to lay down a specific set of criteria for AE, among them the UK Working Group classification [6] and the millennium criteria [7].

Pruritus is the most common feature in AE. The pruritus can be severe, sometimes causing sleep disruption and generalized stress for affected patients and family members. Pruritus leads to scratching which results in secondary skin changes such as excoriation and disrupted skin barrier.

The skin lesions observed in AE vary greatly, depending on the severity of inflammation, different stages of healing, chronic scratching, frequent secondary infections and age. Eczematous lesions usually present during infancy and childhood, but can persist or even start in adulthood. In the first months of life, yellowish desquamation on the scalp may be present followed by eczematous lesions, oozing and crusting preferentially on the cheeks and the chin, usually sparing the perioral region. Cheilitis is common. A significant number of infants develop a generalized eruption, and involvement of the cubital/popliteal fossae is common. During the childhood phase, eczematous lesions frequently involve the flexural areas, the neck, wrist and ankles.

During the adult phase, eczematous involvement of the flexures, neck and hands are typical findings. Additionally, hand eczema or eczematous lesions of the periorbital region are common. Intense pruritus and scratching on persistent eczematous lesions result in thickening of the skin, the so-called ‘lichenification’. Patients with the pruriginous type of AE present with localized or widespread pruritic papules, which are partly excoriated due to intense pruritus.

In all, 50 – 80% of patients with AE have or develop asthma or allergic rhinitis. Type 1 allergies to different allergens are a common feature in patients with AE. Food allergens, such as egg, milk, wheat, soy and peanuts may induce eczematous skin rush in 40% of the children with moderate to severe AE. After the age of 3, children frequently outgrow food allergies but may become sensitized to inhalant allergens such as dermatophagoides pteronyssinus, birch pollen, hazelnut pollen, grass pollen and other common aeroallergens. Epicutaneous application of aeroallergens by atopy patch test on uninvolved skin of patients with AE may elicit eczematoid reactions [8,9].

Serum levels of IgE and specific IgE antibodies directed against environmental antigens can be detected in most AE patients. However, a subgroup of patients exists, in which IgE-mediated mechanisms are not detectable (‘intrinsic type’ [10]). Furthermore, elevated detectable specific IgE antibodies and positive prick test results are not linked to clinically relevant sensitizations in all cases [11].

1.1 Hygiene hypothesis

Prevalence of AE and other atopic allergic disorders were continuously increasing in Western industrial countries [12]. This led to the conclusion that declining family size, improvement in household amenities and higher standard of personal cleanliness reduced childhood infections and contact to bacterial endotoxins at home [13,14]. Reduction of exposure to bacterial endotoxins with increase in hygiene and living standard may result in a skewed development of the immune system and an abnormal response to various environmental allergens which are otherwise innocuous and the lack of antigenic competition led to increased incidence of the phenomena seen in atopy.

These explanations had several supporting observations. Several studies had shown that atopic disorders were less frequent in positive tuberculin responders and bacterial infections reduced the incidence of atopy in children [15,16]. Moreover, the incidence of atopic disease had been shown to be related to the age of entry into the nursery in a large study conducted by Kramer et al. [17] in Germany.
children from small families who entered nursery at a later age (who were less exposed to infections from other children) had higher rate of getting atopic disorders than those who had entered nursery at a younger age. Moreover, further studies found that farmer’s children, who grow up with an increased exposure to bacterial and fungal components, had a significant lower risk to develop atopic asthma [18].

The so-called hygiene hypothesis was explained by cross-regulation between the two subsets of T-helper cells with down-regulation of T\(_{H1}\) cells by release and overproduction of T\(_{H1}\) cytokines and vice versa. Also, increased incidence of atopy was explained by the lack of infections with consecutive reduced stimulation of T\(_{H1}\) cells resulting in increased T\(_{H2}\) cytokine release leading to the inflammation [19]. These observations led to the use of diet supplementation with Lactobacillus CG, marketed as probiotics.

However, it has been stated that the ‘hygiene hypothesis’ works only for respiratory atopy whereas AE does occur less frequently in these conditions [20].

### 1.2 Immune dysregulation in AE

AE may be considered as a cutaneous manifestation of a systemic disorder that gives rise to asthma and allergic rhinitis. These conditions are all characterized by elevated serum levels of IgE and peripheral eosinophilia.

Key effector cells of atopic diseases are T cells, which are divided into various groups (T\(_{H0}\), T\(_{H1}\), T\(_{H2}\), T\(_{H3}\)) according to the type of cytokines they produce [21].

T\(_{H2}\) cytokines such as IL-4, -5, -10 and -13 play an important role in the skin inflammatory response in AE. In consequence of an impaired balance of the CD4-positive T-helper cell populations T\(_{H1}\) and T\(_{H2}\), enhanced IL-4 and -13 production by T\(_{H2}\) cells induces isotype-switching to IgE synthesis. The evidence for a central role of IgE was provided by several studies showing that IgE is expressed on epidermal Langerhans cells (LCs), dendritic cells (DCs) which are overexpressed in lesional skin of AE, and play a central role due to allergen presentation in AE. In lesional as well as in non-lesional skin of atopic patients, epidermal LC were shown to express the high-affinity IgE receptor on the cell surface and carry IgE via the high-affinity IgE-receptor in a significant higher amount compared to skin of healthy subjects [22,23].

Allergen uptake by IgE receptor bearing DCs and consecutive skin homing of cutaneous lymphocyte antigen (CLA)-bearing T cells are assumed to mediate the inflammatory response [24-26].

In addition, release of chemokines and chemotactant factors followed by recruitment of inflammatory cell subtypes is assumed to represent a causative factor for the inflammatory response, leading to development of eczema [27] and improvement of the eczematous lesion has been shown to correlate with reduced chemotaxis of inflammatory cell subtypes [26,27].

Furthermore, due to an impaired epidermal barrier function (as discussed below), aeroallergens known to elicit IgE-mediated reactions are able to penetrate the skin barrier and provoke eczematous lesions. This finding can be used for the diagnosis in AE patients with suspected allergy to aeroallergens by using the atopy patch test [8,9].

Epidermal keratinocytes from AE patients produce a unique profile of chemokines and cytokines [2] following mechanical stimulation, for example, scratching. As compared to psoriasis, molecules such as IL-16, a LC-derived chemotactant cytokine for CD4\(^+\) cells, RANTES, monocyte chemoattractant protein-4 (MCP-4) and eotaxin are overexpressed in atopic skin and may contribute to the chemotaxis of eosinophils, macrophages and T\(_{H2}\)-lymphocytes.

### 1.3 Impaired skin barrier

Inflammatory skin responses with eczematous flares have been assumed to reflect the consequences of the above described immunologic abnormality (the inside-outside view of AE pathogenesis). However, it has as well been proposed that the skin lesions and barrier abnormality are not merely epiphenomena but rather the cause of disease activity (the reverse outside-inside view of disease pathogenesis) [28].

The epidermis and the outermost skin layer (stratum corneum) provide the permeability barrier and is an antimicrobial, antioxidant, UV-filtering, mechanical and sensory interface [28,29]. Moreover, the epidermal barrier has an important role in trapping moisture and preventing dry skin.

Based on the association of inherited abnormalities in the intracellular protein filaggrin expression, AE is well considered as a disorder of epidermal structure and function [30] and a disease of primary barrier failure, characterized by a defective permeability [29,31] and antimicrobial function [32].

Loss of filaggrin, a protein needed for terminal differentiation, provokes a loss of permeability-barrier abnormality, but the exact mechanism is not known. The gene coding for filaggrin was found to be mutated in many patients with AE [30,33,34]. However, it is not clear what drives impaired barrier dysfunction in the skin of patients without a filaggrin mutation. It has been hypothesized that loss of filaggrin could induce corneocyte deformation, but also could be combined with a lack of filaggrin as a substrate for processing polycarboxylic acids, such as pyrrolidine carboxylic acid and trans-urocanic acid. These polycarboxylic acids act as osmolytes, drawing water into corneocytes, partially accounting for corneocyte hydration. Hence, filaggrin deficiency could result in decreased stratum corneum hydration.

A large pool of preformed pro-inflammatory cytokines is stored in the stratum corneum layer and the cytokine cascade helps to restore the barrier function in normal skin [35]. The mediators are released into the lower epidermis if the barrier function is perturbed and because the barrier function is abnormal in AE, cytokine release is sustained and the ongoing cytokine cascade leads to the recruitment of additional, pro-inflammatory mediators (hence, the ‘outside-to-inside’ concept of AE pathogenesis). Additionally, failure of barrier function triggers AE through the increased penetration of haptons, which stimulate immunologic responses [28].
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1.4 Susceptibility to pathogens

Patients with AE are highly susceptible of cutaneous bacterial, fungal and viral infections [1,2,36]. Staphylococcal and streptococcal infections are common complications of atopic lesions. Cutaneous and nasal colonization with Staphylococcus aureus contribute to the exacerbation of AE and the density of S. aureus colonization correlates with clinical severity [37]. Due to a number of defects in the innate cutaneous immunology, colonization with S. aureus is increased. It was found that staphylococcal exotoxins exacerbate AE via T-cell activation not only as superantigens, but to a great extent also as conventional allergens [38]. Moreover, keratinocytes from patients with AE are deficient in their ability to synthesize antimicrobial peptides needed for the innate immune responses against microbes [2] and reduced levels of antimicrobial peptides [39] have been detected in acute and chronic skin lesions of AE compared with lesions of other inflammatory diseases.

A variety of defects in the innate immune system, such as the reduction of antimicrobial peptides in the skin of atopic patients, diminished recruitment of innate immune cells to the skin, epithelial barrier disturbance and defects in pattern recognition molecules of the innate immune system (Toll-like receptors or TLR) may account for the susceptibility of patients with AE to pathogens such as S. aureus, herpes simplex virus and vaccinia virus [32,37,40].

In summary, knowledge about the complex background of AE increases and research on the immunological and environmental level contribute to a better understanding of the pathophysiology of AE.

2. Medical need

AE with its increasing incidence worldwide and its relapsing intermittent course reflects a burden for the affected patients, their families and the society.

Therapy in AE largely consists of topical immunomodulators or steroids. Modification of the hydrocortisone, which was introduced by Sulzberger et al. 1953 into clinical practice, led to the development of more potent topical steroids with the benefit of increased efficacy but the disadvantage of increased side effects mostly due to skin atrophy. In the past decade, two new agents, topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, were licensed for topical eczema treatment and were found not to cause skin atrophy. This favors their use in body areas with thin skin such as the eyelid region, the perioral skin, the genital area or the inguinal fold. Concerns about the adverse side effects of topical steroids and warnings about the potential toxicity associated with prolonged use of these immunosuppressive calcineurin inhibitors could stimulate search for alternative forms of therapy. Despite recognition that AE is one of the most frequent chronic skin diseases, there is a high unmet need for immunomodulating, anti-inflammatory compounds that can be topically administered.

There is also a high level of unmet need for safer systemic therapies and effective drugs against itch. Recent advances in immunology and increased understanding of the basic pathophysiology as well as the advent of the genetic engineering techniques have led to the development of a new group of drugs referred to as biologicals, which are proteins against cell surface markers, cytokines and adhesion molecules. Currently biologicals are available for psoriasis, another inflammatory skin disease and these available agents target either T cells or antigen presenting cells or block the inflammatory action of TNF-α, a pro-inflammatory cytokine. Their efficacy in AE needs to be investigated. Furthermore, cytokines or chemokines play a critical role in perpetuating inflammation in atopic skin. Several specific cytokine and chemokine inhibitors are in development for the treatment of asthma – another atopic disease with similar pathogenesis – and these medications may be effective in the treatment of AE as well.

Despite recognition that AE is a major public health concern, many treatment modalities are not based on evidence. The chronic course of AE and the lack of cure by specific medications lead to treatment modalities with dubious efficacy. Thus, recently the ETFAD/EADV (European Academy of Dermatology and Venerology) eczema task force developed guidelines for the diagnosis and treatment of AE based on literature review and repeated consenting group discussions [41]. Although there have been therapeutic advances in the past decades, representative, randomized, placebo-controlled studies evaluating the efficacy and safety of different treatment modalities are not available for many therapeutic strategies, especially the basic application, and this needs to be addressed in future studies.

3. Existing treatment

The treatment of AE requires a complex approach. Primarily, irritants and specific immunologic stimuli such as environmental allergens, such as food or inhalants, have to be identified and need to be avoided as they are known to induce or trigger eczematous lesion. Irritant factors such as chemicals or physical agents may also complicate the disease and have to be avoided. Psychosomatic counseling may help to cope with stress.

3.1 Topical treatment of AE

3.1.1 Emollient therapy

Hydration of the skin is a key part of the management and helps to improve the dryness, the pruritus and restore the disturbed skin barrier. Evidence-based proofs for the use of emollients, however, are limited, but clinical experience as well as a few randomized controlled trials showed that adjunctive emollient therapy may reduce the need for treatment and related side effects and may lead to reduction of steroid therapy [42,43].
3.1.2 Anti-inflammatory therapy

3.1.2.1 Topical corticosteroids

Topical steroids are the mainstay in treating acute flares of AE. In 1953, Sulzberger et al. reported about successful treatment of eczematous lesions with topical hydrocortisone, leading to widespread use and modification of the basic molecular structure of hydrocortisone with development of more potent topical compounds. Widespread use of these more potent steroids with excellent short-term efficacy, however, led to the knowledge of the disadvantage of adverse effects including skin atrophy, striae, telangiectasia, acneiform eruptions and the risk of absorption, with potential systemic effects in long-term use or in widespread application.

However, topical steroids are first-line anti-inflammatory treatment, provide rapid relief and are used for short periods (5–7 days) to settle eczema flare-ups. Corticophobia is a major problem and leads to suboptimal treatment of eczematous lesions in some cases. When used for prolonged periods, topical glucocorticoids can cause side effects such as skin atrophy including an increased tendency to develop tachyphylaxis and rebound flares following discontinuation of therapy [44]. Therefore, topical steroids should be used with care especially in areas with thin skin such as the periorbital or the genital region and in children.

Non-fluorinated steroids are normally less potent and show less adverse effects. Consequently, non-fluorinated steroids – such as hydrocortisone valerate, hydrocortisone butyrate and mometasone furoate – are less prone to provoke local or systemic side effects in long-term application. Therefore, non-fluorinated corticosteroids are used more often in patients with chronic disease and in children [45]. However, there are reports that non-fluorinated corticosteroids are more likely to induce contact allergy than fluorinated ones [46].

Fluorinated steroids, such as dexamethasone, trimacronolone, fluocortolone, flumethasone, betamethasone-valerate or diprostone are those steroids which are substituted with one or more fluorine atoms in any position to enhance the efficacy. The term ‘topical fluorinated steroid’ is frequently used as a synonym for a potent steroid. In recalcitrant eczematous lesions, absorption and efficacy of topical steroids can be increased by occlusive therapy or wet wraps.

Though acting immunosuppressive, it should be noted that even in long-term, topical use of steroids with no increased risk of either lymphoma and sun-induced skin cancers has been reported.

Topical steroids bind to an intracellular glucocorticoid receptor (GCR) that forms a complex (corticosteroid/GCR complex) on ligand binding and affecting a wide variety of cells. On ligand binding, the corticosteroid/GCR complex translocates into the nucleus inducing gene transcription by binding of GCR dimers to glucocorticoid response elements in the promoter regions of target cells. This process, known as transactivation, is responsible for many side effects of glucocorticoids. The second major action of the GCR is the ligand binding to various transcription factors, a process called transrepression, which is independent of GCR-DNA binding. In this process, ligand-bound GCR binds to various transcription factor, such as NF-κB, and activator protein-1 mediated by protein–protein interactions inhibiting the transcriptional activity of various genes encoding pro-inflammatory proteins such as cytokines (IL-1, IL-2-IL-3, IL-4, IL-5, IL-6, IL-11, IL-13, TNF-α and GM-CSF), chemokines (IL-8, RANTES, macrophage inflammatory protein 1-α, MCP-1, MCP-3, MCP-4 and eotaxin) and adhesion proteins (ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) and E-selectin).

On the cellular level, further studies demonstrated that topical corticosteroids reduce viability and function of LC and DC of skin and lymph nodes, contributing to a reduction in T\textsubscript{H}1-promoting cytokines. In vitro studies of mononuclear cells obtained from healthy volunteers, corticosteroids have been shown to cause apoptosis of monocyte-derived DC precursors and inhibit expression of DC-specific antigens such as CD83 and CD86 and the ability of CD to activate primary CD4+ T-cell proliferation [47] and have an adverse effect on IL-12 expression on LC/DC.

3.1.2.2 Wet wraps

Application of damp tubular elasticized bandages and occlusive dressing to the limbs at night promotes skin hydration and the absorption of emollients and topical corticosteroids. These wet wraps are effective in severe childhood eczema with exudates. First, steroid ointment with plenty of moisturizing emollients are applied on acute flares; over that, the second outer layer is applied dry.

3.1.2.3 Topical calcineurin inhibitors

Topical tacrolimus and pimecrolimus are approved for the treatment of AE in the EU from 2 years of age onwards [48]. Many placebo-controlled clinical trials for short- [49] and long-term use [50–52] have shown both topicals to be effective.

In contrast to topical pimecrolimus cream and tacrolimus ointment, systemically administered tacrolimus and cyclosporin A have been shown to induce systemic immunosuppression, thus, increasing the risk of malignancies and UV-light-induced cancers in patients having undergone organ transplantation. Additionally, cases have been reported in which cancers have developed at sites of prolonged use of topical application or in draining lymph nodes. However, some of the reported cases of ‘recalcitrant’ eczema were in fact malignant disorders, such as Bowen disease, Paget disease or parapsoriasis en plaque. Therefore, it has been recently recommended to biopsy ‘recalcitrant’ eczema prior to treatment with topical calcineurin inhibitors.

All these findings prompted the FDA to reconsider the risk/benefit profile of the topical use of calcineurin inhibitors and add a ‘black box warning’, as these agents were widely used in children with AE. However, a scientifically based, critical statement regarding this warning, authored by many leading European dermatologists, was published in 2005 [53].
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reporting that neither tacrolimus or pimecrolimus have been associated with increased malignancy risk in clinical studies [54] and that there is no evidence of systemic immunosuppression [53]. In years of usage in > 5 million patients using pimecrolimus cream and > 1.7 million patients using tacrolimus ointment, the safety of both of these treatments has been established in many studies. Clinical data did not indicate an increased risk for lymphoma over the period of 6 years. However, the increased photocarcinogenicity risk in solid organ transplant patients under medication with the oral calcineurin inhibitor cyclosporine and experimental data in immunodeficient hairless mice led to the recommendation of UV-protection, for example, with sunscreens in patients under topical anti-inflammatory therapy.

In contrast to topical glucocorticoids, topical calcineurin inhibitors do not lead to skin atrophy and may, therefore, be used for the regions where low potency steroids are used due to fears of skin atrophy, such as the eyelid eczema, the perioral skin and the genital region.

On the molecular level, both tacrolimus and pimecrolimus selectively inhibit the activation of T cells by inhibiting calcineurin through binding with high affinity to the 12 kDa macrophilin and inhibit the phosphatase activity of the calcium-dependent serine/threonine phosphatase, calcineurin. Calcineurin inhibits the dephosphorylation of the transcription factor, nuclear factor of activated T-cell protein. The inactive form of nuclear factor of activated T cells cannot enter the nucleus, and the activation of transcription of various T111 and T112 cytokine genes is inhibited. Pimecrolimus potently inhibited the proliferation of antigen-stimulated T cells and the production and release of inflammatory T111 and T112 cytokines. Moreover, it was shown that pimecrolimus inhibited the expression of the cell surface co-receptor CD134, which is increased in activated T cells and inhibits their apoptosis [54].

It was demonstrated that pimecrolimus, in contrast to steroids, does not suppress viability and function of LC in animals and humans [47]. These and other studies [55,56] led to the assumption that calcineurin inhibitors act more selectively on the skin immune system.

3.1.2.4 Topical anti-inflammatory therapy: reactive versus proactive treatment

Due to potential side effects following chronic use, topical corticosteroids are not used for maintenance therapy. The common traditional treatment concept for AE was based on the use of anti-inflammatory agents for symptomatic skin on a ‘needed’ basis and a long-term treatment with daily application of emollients with or without antibacterial ingredients. This so-called ‘reactive treatment’ was eventually combined with UV-phototherapy and antihistamines.

However, several studies demonstrated that normal appearing skin in AE patients is not normal. First of all, in eczematous lesions as well as in normal appearing, non-lesional skin epidermal barrier dysfunctions [29] could be detected. Immunohistological examination in patients with AE revealed signs of minimal disease with hyperkeratosis, intercellular edema and slight dermal lymphocytic infiltrate in non-lesional skin [57]. Wollenberg et al. found significantly elevated high-affinity IgE receptor expression even in non-lesional, normal appearing, atopic skin [58].

Second, increased permeability of large protein allergens penetrating the disturbed epidermal barrier in normal appearing skin elicited eczematous lesions [8,9,29]. Furthermore, an analysis of the epidermal lipids essential for skin barrier function showed decreased levels for extractable long-chain fatty acids in lesional as well as in non-lesional skin of AE patients. Several loss of function mutations of the filaggrin gene leading to a barrier defect have recently been detected in high association with AE [50].

These findings confirmed that normal looking, non-lesional skin is characterized by a clinically-meaningful, barrier-dysfunction defect, a subclinical inflammation, suggesting that maintenance anti-inflammatory treatment may be required to prevent relapses. Several studies using topical corticosteroids showed that long-term control can be maintained with twice weekly therapy. An alternative treatment approach, the so-called ‘proactive treatment’ [59,60] starts with an intensive topical anti-inflammatory therapy until clearance of lesions followed by long-term, low-dose, intermittent application of anti-inflammatory therapy, especially TCI, to the previously affected skin together with daily application of emollients to unaffected areas.

3.2 Phototherapy

Phototherapy is effective in treating refractory AE. This treatment may be administered as UVA, especially UVA-1, UVB or combined treatment [61,62]. Psoralen administered topical by bathing followed by UVA treatment (PUVA phototherapy) may be a treatment option in patients with extensive refractory disease.

Recent studies have underlined the efficacy of suberythemal UVB-phototherapy in the treatment of AE, by disrupting the permeability barrier and regulating the AMP expression [63-65]. The beneficial effect of the low dose UVB therapy seems to depend on the activation of the cutaneous vitamin D system [63]. UVB phototherapy in appropriate physiological doses seems to protect from microbial infections by inducing the innate immune system and releasing cutaneous AMPs, but suppressing the adaptive immune system [65].

3.3 Tar preparations

Tar has anti-inflammatory and antipruritic effects on the eczematous lesions. They are traditionally used as therapy. The disadvantages of tars are their odor and dark staining color. Covering the treated areas can decrease these problems. Bituminosulfonates (e.g., ichthyol) do not have the carcinogenic risk of tars and are used as antipruritic and anti-inflammatory agents in chronic eczema lesions.
3.4 Antihistamines

Therapy with systemic antihistamines is traditionally used in acute flares of AE. Though being used widely, there are a only few controlled studies [41,66]. Thereby, sedative H₁-antihistamines such as hydroxyzine and diphenhydramine are considered to be more effective than recently developed less sedative antihistamines. Though a direct effect of newer non-sedating H₁-receptor blockers on eczematous lesions could not be shown in the few controlled studies, the older sedative antihistamines are used to reduce pruritus and permit sleep in acute phases of the disease.

An evidence-based review of the efficacy of antihistamines in relieving pruritus in AE revealed that, although antihistamines are frequently used, little objective evidence exists to demonstrate their efficacy and the majority of trials are flawed in terms of the sample size or study design [67]. Oral sedative antihistamines may provide benefit to patients who have poor sleep secondary to pruritus [68]. Ongoing studies investigate the blockade of alternative histamine receptors which may be important in AE.

3.5 Anti-bacterial and antymycotic therapy

Patients with AE are more prone to skin infections (bacterial, fungal and viral). Bacterial superinfections cause deterioration of the skin lesions with crusting, oozing and diffusive skin redness. However, patients with severe AE may improve but not be cured by antistaphylococcal treatment. Antibiotic eradication may, therefore, with regard to increasing prevalence of antibiotic resistance, not always be an appropriate long-term strategy.

Topical antiseptics such as triclosan, chlorhexidine or crystal violet or antibiotic skin creams (e.g., fucidic acid) and occasionally oral antibiotics are prescribed to treat acute flares with clinical signs of bacterial impetiginization. Topical application of muporicin may improve atopic skin lesions; however, continuous use may lead to development of muporicin-resistance. Thus, topical use of mupiricin has not been recommended [69]. The use of gentian violet as a topical agent led to improvement in S. aureus colonized AE [70]. Topical application of retapamulin also led to improvement of atopic skin lesions [71]. A recent single-center, randomized controlled trial investigated topical triclosan creams and showed that the antiseptic agent resulted in clinical improvement and blood pressure. A maximum course of 6 months is recommended as toxicity, predominantly renal, limits its chronic use. Rebound phenomenon may be seen if cyclosporine is tapered or discontinued. Due to risk of antibiotic resistance and due to potential risk of allergic sensitization, long-term use of systemic and topical antibiotics is not recommended. Silver-coated textiles have been shown to decrease the staphylococcal colonization and improve eczematous skin lesions [77].

3.6 Systemic immunosuppressive therapy

Most patients with AE respond to conventional therapies with topical emollients, topical corticosteroids, topical calcineurin inhibitors, systemic antihistamines and abstinence from potential trigger factors. However, in patients with severe manifestation of the disease in whom corticosteroid resistance contributes to treatment failure, therapy directed for correcting the immune function is suggested. Prednisone, cyclosporine or azathioprine may be used in these patients with widespread, incapacitating eczema which is not responding to optimized topical therapy.

3.6.1 Systemic steroids

Systemic steroids are controversial in the treatment of AE. In cases of severe, incapacitating eczema systemic steroids may be used as a short-term solution to interrupt acute phases in adult patients. Due to side effects, long-term use of systemic steroids is not recommended in AE. Patients with AE often exhibit the rebound phenomenon with exacerbation of the eczematous lesions when systemic steroids are tapered or discontinued. Systemic steroids should be avoided in preadolescents.

3.6.2 Cyclosporine A

Cyclosporine A is a potent systemic calcineurin inhibitor and is the most established systemic immunosuppressant agent in patients with AE and widespread, severe, recalcitrant disease who has failed topical treatment. Analogous to the topical calcineurin inhibitors, pimecrolimus and tacrolimus, cyclosporine inhibits the activation of T cells by inhibiting calcineurin-dependent signal transduction.

Patients need close monitoring (full blood count, renal function and blood pressure). A maximum course of 6 – 9 months of cyclosporine treatment is recommended as toxicity, primarily renal, limits its chronic use. Rebound phenomenon may be seen if cyclosporine is tapered or discontinued. Due to concerns of development of skin cancer, phototherapy is not recommended during administration of systemic cyclosporin.
3.6.3 Antimetabolites

Methotrexate can be used to treat widespread but milder, recalcitrant disease, it is generally not effective for more severe cases. Mycophenolate mofetil, a purin biosynthesis inhibitor that has also been utilized for recalcitrant AE, although the potential for systemic toxicity restricts the use of antimitabolites and requires close monitoring. Mycophenolate mofetil may be used in AE in adult patients if therapy with cyclosporine is contraindicated. Mycophenolate mofetil (CellCept®, Roche Pharmaceuticals, Nutley, NJ, USA) is a noncompetitive inhibitor of inosine monophosphatase dehydrogenase and inhibits de novo purine synthesis. Currently approved for the prevention of organ rejection, its list of ‘off-label’ dermatologic indications continuously grows [78]. In a pilot study with 10 patients with severe refractory AE it appeared to be an effective treatment.

3.6.4 Azathioprine

Several open studies showed that azathioprine is effective in moderate-to-severe AE [79,80]. A double-blinded, randomized controlled trial of 63 patients showed efficacy of azathioprine monotherapy in AE and pointed to therapeutic importance of the thiopurine methyltransferase (TPMT) polymorphism, a key determinant of azathioprine-induced myelotoxicity, by using TPMT enzyme activity [81]. Patients with homozygous or heterozygous TPMT activity often develop profound, myelotoxicity with azathioprine [82]. Therefore, in the above mentioned trial, patients with heterozygous range TPMT activity received azathioprine in a reduced dose.

Azathioprine may be an effective treatment in AE, which is inadequately controlled by topical steroids and emollients. Gastrointestinal symptoms such as nausea, leukopenia and hypersensitivity may occur. The mechanisms of action of azathioprine in AE are unknown and might be restricted to lymphocytes. In *in vitro* studies revealed that azathioprine is cytotoxic to and impairs LC function [83]. The metabolism of azathioprine is complex and several immunosuppressant metabolites might modulate immune function [84].

Azathioprine may be used in AE if therapy with cyclosporine is contraindicated; however, limited possibility to examine TPMT polymorphism will restrict its use.

4. Current research goals and scientific rationale

In the past decade, several key steps were described in the maintenance of a vicious circle of AE associated with deviated T lymphocyte and LC activation, effects leading to weakened TH1 immunity and IgE overproduction.

The understanding of the pathogenesis of AE has advanced during the past decades; however, the detailed mechanisms of AE still remain unknown. Attempts to understand the mechanisms through animal models have proven difficult [40]. An important question is which factors primarily promote the disease in contrast to factors which act secondarily as a consequence of modification on the genetic, immunological and environmental levels. It is furthermore necessary to characterize the key immune pathways leading to AE. The role of allergens and microbes in the initiation and progression of AE also requires further classification.

4.1 Genetic background

AE is a clinically and genetically heterogeneous disease. Atopy is a common finding in patients with AE and their families, which documents the genetic background in these diseases. AE is not a monogenic disease, but a complex disease with several genetic factors [85] contributing to the pathophysiology. Efforts to define gene regions characteristic for AE or to predict severity and course of AE based on the genetic repertoire provided heterogeneous results and were complicated by the genetically complex constellation [86-88].

Genes predisposing to AE fall into two broad categories: there are skin-related genes that affect barrier function and, further on, there are atopy-related genes that affect the tendency towards immune deviation in the direction of allergy. Polymorphisms in the filaggrin gene, an important protein which is essential to maintain the formation of stratum corneum barrier function, and changes in the gene for IL-4 and its receptor are all associated with AE [30,33]. Loss of function mutations in the filaggrin gene was found to be associated with AE and specific clinical features and subforms of AE were shown to be associated with these mutations [89,90]. In the context of a genetically-determined disturbed skin barrier in AE, association with polymorphism in the SPINK5 gene were described [89], though no association has been found in one study [91].

Knowledge of an individual's risk alleles could be used to tailor therapy and to identify individuals at risk for progressive sensitization, allowing early intervention to improve barrier function. Epigenetic changes may explain why some individuals develop AE later in life, and the environment also plays a critical role.

4.2 Immune deviation

TH10 cells are the naïve T cells whose polarization occurs through the release of cytokines from the cells of the innate system such as macrophages, basophils, eosinophils, mast cells and NK cells. TH11 cells produce IL-1, IFN-γ, which stimulate macrophages and cytotoxic T cells. TH12 cells produce lymphokines that stimulate B cells to proliferate and produce antibodies. These lymphokines are IL-4, -5, -6 and -13. The regulatory cells of a TH13 type are now recognized to be important in regulating or switching off the immune response by production of IL-10 or TGF-β [21].

Recent studies have shown that mediator substances and pro-inflammatory cytokines appear to be important for the pathogenesis of AE. In particular, AE has been shown to be associated with increased TH12 (IL-4, -5, -13) cytokine production that causes activation of eosinophils and T cells
and production of chemokines (e.g., eotaxin, RANTES, TARC). Thus, selective inhibition of the inflammatory cascade has become possible with novel therapeutic approaches which have been developed recently. Such approaches comprise treatment with recombinant anti-inflammatory cytokines, treatment with T$_{H1}$ inducing cytokines, inhibitors of IgE, and antagonists of pro-inflammatory cytokines (e.g., IL-4 and -5) and their receptors.

These gene-technologically prepared biological agents (‘biologicals’) present new therapeutic tools in the treatment of severe psoriasis and other inflammatory diseases such as rheumatoid arthritis and Crohn’s disease. A number of case reports and pilot studies with these available and approved medications have been published recently reporting about therapeutic trials in AE. However, to date representative, randomized, placebo-controlled studies evaluating the efficacy and safety in AE are still not available. Moreover, the clinical value of these novel therapeutic approaches in AE remains to be determined. In particular, long-term efficacy and safety of immunomodulatory therapy has to be studied in more detail.

5. Competitive environment

5.1 Skin care

There is limited evidence-based proof for the use of emollients in AE [41,42]. A lack of important stratum corneum intercellular lipids and an inadequate ratio between compounds (cholesterol, essential fatty acids, ceramides) as well as the newly described filagrin defect [34] enhance trans-epidermal water loss leading to epidermal micro-fissuring. Recent genetic studies point to the primary role of a defective barrier to water loss and microbial invasion which may provoke eczematous lesions in affected patient. These findings led to the rationale for barrier repair therapy [28,35]. With increasing evidence supporting the role of abnormal permeability barrier function [28-31], emphasis has been placed on restoring the physiologic barrier functions of AE by medications that claim to assist barrier repair. An increasing number of studies have shown the efficacy of related therapies.

In preliminary studies, addition of a ‘ceramide dominant’ emollient leads to clinical improvement and decreased transepidermal water loss as a result of improvement of the stratum corneum integrity. EpiCeram® is a ceramide-dominant, triple-lipid barrier repair formulation based on optimization of barrier lipid composition that is so far only available in the US. A recent randomized, controlled multi-center trial in 121 patients with AE investigated its efficacy compared to fluticasone propionate 0.05% cream. The investigators described reduced disease severity and decreased pruritus and concluded that this formulation could represent an effective primary or ancillary therapy especially for pediatric patients with AE [92].

Also, adjuvant treatment with an emollient containing N-palmitoylethanolamine has proven to be beneficial (ATOPA study) [43]. MimyX®, launched in the US, also claims barrier repair functions. Physiogel® AI Cream contains the same ingredient (cannabinoid N-palmitoylethanolamine) and has been studied in an open-label trial [43], which demonstrated significant improvement in patients with AE.

MAS063DP, also known as Zarzenda® or Atopiclair®, is another hydrolipidic cream with barrier repair claims. It is available in the US, in Europe and Israel. It contains hyaluronic acid as well as vitis vinifera (grapevine) extract with antioxidant and antiprotease activity. A randomized, vehicle-controlled study revealed efficacy of MAS063DP in children and adults with AE [93,94].

5.2 Allergen-specific immunotherapy

Allergen immunotherapy is one of the oldest treatment forms (the first ‘biological’) against sensitizations in allergen-induced asthma or allergic rhinoconjunctivitis. Subcutaneous immunotherapy with allergen extract adsorbates is currently the most widely used treatment modality worldwide. Either subcutaneous or sublingual immunotherapy (SLIT), which is prescribed with increasing frequency, represents the only disease modifying treatment modalities and the only causal therapy for allergic diseases apart from allergen avoidance.

In AE patients, aeroallergens are not only capable to provoke immediate allergic reactions but also delayed-type reactions and eczematous lesions [8,9]. So far, allergen-specific immunotherapy has not been recommended due to concerns of lesion exacerbations or potential relapses of latent AE. However, reports and studies about the benefit of allergen immunotherapy in AE exist [95-97]. Recent studies reveal that allergen-specific immunotherapy might represent a therapeutic option for the treatment of sensitizations in AE patients [98].

The immunological mechanism responsible for the clinical efficacy is associated with induction of T regulatory cells, increase in allergen-specific IgG4, increase in IL-10 and TGF-β production as well as downregulation of the T$_{H1}$-response [99]. Allergen immunotherapy decreases recruitment of mast cells, basophils and eosinophils in the skin and mucosa following exposure to allergen blocking immediate and late phase responses [100]. Adverse events include common local site reactions such as oral mucosal reactions in SLIT to rare life-threatening anaphylaxis and death.

Modification of allergen extracts has been developed as a result of the effort to develop safer and more effective allergens. Allergoids are chemically modified allergen extracts and have been developed in the effort to reduce allergenicity while preserving immunogenicity.

Adjuvants, such as immunostimulatory oligonucleotide sequence of DNA containing a CpG motif (CpG) and 3-deacetylated monophosphoryl lipid A (MPL), target TLR and influence the T$_{H1}$/T$_{H2}$ cytokine balance. TLR 9, which is expressed on plasmacytoid DCs, is the receptor for CpG-DNA and activation leads to production of IL-10, IgG isotype switching and other T$_{H2}$ cell immune responses [101]. Tolamba, a TLR9 agonist, is a CpG adjuvant that is linked to the major
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Ragweed allergen. However, the lack of measurable disease activity during ragweed season in any of the study groups during a 2 year study made it impossible to measure the therapeutic effect; therefore, tolamba development was discontinued.

MPL, another adjuvant used in allergen immunotherapy contains monophosphoryl lipid A, derived from lipopolysaccharide of salmonella minnesota R595, which is a TLR-4 agonist and induces Th1 cytokines in human studies. Allergoids containing MPL adjuvants have been shown to provide significant improvement in clinical and immunological parameters in patients with seasonal rhinitis, another atopic disorder often associated with AE. One major concern and potential adverse effect in Th1 inducing adjuvants is the autoimmunity. In the past 4 years, double-blind placebo-controlled clinical trials designed to study the efficacy and safety of MPL in the treatment of allergic rhinitis have been conducted and treatment was effective and tolerated well. In addition to clinical immunotherapy trials, MPL is used as an adjuvant in licensed vaccines for many years (e.g., Cervavix® vaccination for prevention of HPV infection, GlaxoSmithKline, Philadelphia, PA, USA) and has been tolerated well.

So far, recent studies showed that specific immunotherapy might lead to a significant improvement in clinical symptoms, combined with immunological changes [95,96,98]. In summary, further studies are warranted to evaluate the benefit of the different therapeutic modalities of specific immunotherapy and the immunological changes induced by specific immunotherapy in AE.

5.3 Probiotics

Rising evidence of AE in industrialized countries was explained by reduced exposure to immunostimulation by dirt in clean environment, reduced family size and reduced exposure to childhood infections and microbes, which play a crucial role in the maturation of the host immune system during the first years of life. Clean and hygienic environment is supposed to lead to a skewed development of the immune system resulting in an abnormal response to various environmental allergens. Allergic responses may arise if there is absence of microbial exposure while the immune system is still developing [102].

Therefore, one hypothesis is that feeding children with bacteria of healthy gut microflora could reduce incidence of atopy [103]. Some studies indicate that taking dietary supplement containing viable bacteria (probiotics) may help reduce the severity and extent of the disease [104]. It has been suggested, as these viable microorganisms may modulate TLR and the proteoglycan recognition proteins of enterocytes, leading to activation of DC and a Th1 response. Pediatric studies suggested that the probiotic use in children with AE results in the increase of IFN production and decrease of IgE- and antigen-induced TNF-α, IL-5 and IL-10 secretion. However, a review of 13 studies of probiotics for treating established eczema did not show a clinically worthwhile benefit [6].

Recently, it has been suggested that topical application of probiotics and nonpathogenic bacterial compounds might be promising [105]. More studies are needed to predict whether these supplements may be beneficial in preventing AE. In summary, the efficacy of probiotics in the prevention and treatment in AE has not been evaluated conclusively to date, but may be worthwhile studying. Patients and parents should be aware that – to this day – unequivocal benefit could not be found.

5.4 Intravenous immunoglobulins

Intravenous immunoglobulins (IVIG) treatment has been shown to be beneficial in a few open studies but evidence of effectiveness is still lacking [106]. An open-label study investigating 10 patients with AE did not confirm a clear clinical benefit [107]. In another study of six patients, IVIG therapy resulted in a clinical improvement [108]. Clinical efficacy of high dose IVIG therapy is transient and its effectiveness in relation to the expensive treatment must be evaluated in further studies.

Currently, there is no role for IVIG in the treatment of mild-to-moderate AE. A few open studies did not either confirm a clear clinical benefit [107] or show clinical improvement [108]. Further studies will be important to refine the current knowledge base for potential use of IVIG.

5.5 Leukotriene inhibitors

Leukotriene inhibitors are registered for the treatment of asthma. Because asthma and AE have a similar pathogenesis, leukotriene inhibitors such as montelukast or zafirlukast may have a role in the treatment of AE, but there are only single reports describing the successful use in the treatment of AE. In a study investigating the efficacy of montelukast against conventional therapy with topical steroids in 32 patients, therapy with montelukast resulted in decrease of SCORAD and serum levels of eosinophil cationic protein (ECP) [109]. In study of 2005, no effect of treatment with montelukast was observed [110]. Thus, with controversial study results, leukotriene inhibitors may be a potentially useful agent in severe AE. Larger studies need to be undertaken to more fully characterize the use of leukotriene inhibitors in the treatment of AE.

5.6 Targeted immunomodulating therapies

Most of the traditional therapies aim at clinical improvement without targeting the factors that primarily promote AE. Biologic agents hold the promise for a more targeted and less toxic approach to systemic therapy. A recent study reviewed publications reporting the use of biologicals in the treatment of AE. These diverse biologicals were primarily approved for other diseases such as psoriasis. The safety of biologics in the treatment of AE was confirmed, as few side effects such as thrombocytopenia and no type I immediate hypersensitivity reactions were reported among 261 patients with AE exposed to biologic therapy [111].
5.6.1 Anti-IgE treatment

Recently, omalizumab has been shown to be effective in treatment of severe allergic asthma and severe allergic rhinitis, and thus has been approved in the US to treat moderate-to-severe allergic asthma in adults and children 12 years and older (Table 1). Omalizumab has been shown to be effective in patients with moderate-to-severe AE [112]. The most common adverse events are injection site-pain, but there are also reports about anaphylaxis in 0.09% of patients receiving omalizumab [113].

Anti-IgE (omalizumab) therapy showed beneficial effects in 6/11 patients with AE [114]. However, divergent results have been reported for its efficacy in patients with refractory AE and IgE levels far exceeding those of patients with asthma [114,115]. Due to high serum IgE levels seen in patients with AE, the registered dose for asthma might not be sufficient in patients with high elevated IgE levels and further studies are under way to examine the benefit of omalizumab in AE patients.

In summary, anti-IgE treatment may have a potential role in the treatment of AE, but studies to date have not been conclusive. However, the effect may have to be determined and may depend on the target population, for example, depend on the levels of serum IgE which can diverge significantly from patient to patient.

5.6.2 Inhibition of T-cell responses

T_{H}2 cytokines play an important role in orchestrating and perpetuating the inflammatory response in AE, which suggests that blocking the release or the effects may be useful to diminish inflammation.

Approaches resulting in reduced T-cell activation used agents such as alefacept and efalizumab (Table 1). Alefacept, a fusion protein of lymphocyte function antigen-3 (CD58) which inhibits co-stimulation and induces apoptosis of T cells, has been shown to be effective in patients with moderate to severe AE [116,117]. In all, 10 patients with moderate-to-severe AE have been treated in an open-label pilot study with 12 weekly intramuscular injections. The study revealed clinical improvement in all 10 patients and decreased numbers of skin T cells as well as reduced T-cell activations with therapy [116]. Also efalizumab, an antibody which inhibits T-cell recruitment, resulted in improvement of AE symptoms. Efalizumab was shown to be effective in 6/10 patients with severe AE [111]. However, efalizumab was withdrawn from the market due to potential neurological complications seen in patients with psoriasis in long-term use and is now no longer available.

5.6.3 Inhibition of pro-inflammatory cytokines

Common drugs that inhibit cytokine synthesis are glucocorticoids, cyclosporine A and tacrolimus.

Pro-inflammatory cytokines, particularly IL-1β and TNF-α, may amplify inflammatory response in atopic diseases by amplifying inflammation through the activation of NF-κB and other transcription factors. These findings suggested that blocking TNF-α could have beneficial effects, particularly in severe AE.

5.6.3.1 TNF-α blocking agents

TNF-α blocking agents have been used in rheumatology primarily in the treatment of rheumatoid arthritis and in the treatment of psoriasis, and these agents have been extensively studied in the above mentioned diseases. In a preliminary study of nine patients with moderate or severe AE, therapy with infliximab, (anti-TNF-α mAb) significantly improved all clinical parameters, but this improvement was not sustained through maintenance therapy [118]. The investigators concluded that infliximab monotherapy may be an additional therapeutic option for the management of refractory severe AE. Further studies are warranted to investigate the efficacy of anti-TNF-α antibodies in AE.

5.6.3.2 Anti-IL-4 strategies, soluble IL-4

Anti-IL-4 plays an important role for the synthesis of IgE by B-lymphocytes. IL-4 promotes differentiation of T_{H}2 cells and, therefore, mediates important pro-inflammatory functions in atopic disorders such as induction of the IgE isotype switch, expression of VCAM1, promotion of eosinophilia transmigration across endothelium and differentiation of T_{H}2 lymphocytes leading to cytokine release as a critical site in atopic disorders.

In atopic diseases, another therapeutic approach is to inhibit IL-4R with a mutated form of IL-4, which binds and blocks to the IL-4Rαa and IL-13Rα1, consecutively inhibiting both IL-4Rα and IL-13Rα1, as these two closely related cytokines signal through a shared surface receptor, IL-4Rα [102]. Also, endogenous inhibitors of STATS, suppressor of cytokine signaling-1, are potent inhibitors of the IL-4 signaling pathway and offer novel therapeutic approaches (Table 1) [119].

In a Phase I/II randomized, placebo-controlled trial, efficacy of soluble IL-4 receptor for the treatment of asthma was described [120]. Thereby, nebulized administration of rhuIL-4R once weekly (Nuvance™ Immunex) resulted in a clinical improvement of asthma. Another humanized anti-IL-4 antibody, Pitakrinra (SB240683, Pascolizumab®, BAY16-996) is a recombinant IL-4 variant that binds IL-4Rα receptor inhibiting the binding of both IL-4 and -13. Two trials of pitakrinra administered subcutaneously or via nebulizer showed some clinical efficacy in asthmatic patients [121], and further studies are warranted to test the benefit in AE. According to current knowledge, to date there are no reports for the use of anti-IL-4 mAbs in patients with AE, and the fact that in asthmatic patients nebulized preparations have been used leads to the suggestion that these agents should be tested for their efficacy in topical administration.

5.6.3.3 Anti-IL-5

T_{H}2 cells produce IL-5, a cytokine which accounts for eosinophilia, as eosinophil development from hematopoietic
progenitors is regulated mainly by IL-5 which in turn has a selective role in eosinophil maturation, differentiation, mobilization, activation and survival. Eosinophils are important effector cells in atopic diseases and deposition of their toxic granule proteins (eosinophil degranulation) such as ECP are assumed to be an important process in mediating the tissue damage in this disease. ECP serum levels are highly elevated in patients with AE.

Anti-IL-5 is a drug that is effective in patients but is not yet approved by the FDA (Table 1). Mepolizumab is a fully humanized, anti-IL-5 monoclonal immunoglobulin antibody (IgG1, mAb) and blocks binding of human IL-5 to the α chain of the IL-5 receptor complex expressed on the eosinophil cell surface. In preliminary studies of patients with hypereosinophilic dermatitis and atopy, mepolizumab had few side effects and lowered blood eosinophil levels [122,123] but had moderate clinical effect in patients with atopic eczema in a short-term study with two infusions per patient [123]. Unfortunately, a long-term study has not been performed with anti-IL-5 antibodies after these promising results. Subsequent studies suggested that mepolizumab may have substantial clinical value in patients with hypereosinophilic dermatitis and atopy, mepolizumab had few side effects and lowered blood eosinophil levels [122,123] but had moderate clinical effect in patients with atopic eczema in a short-term study with two infusions per patient [123]. Unfortunately, a long-term study has not been performed with anti-IL-5 antibodies after these promising results. Subsequent studies suggested that mepolizumab may have substantial clinical value in patients with hypereosinophilic syndrome [124]. These initial reports led to an international multi-center study, which showed that treatment with mepolizumab can result in corticoid-sparing for patients with the lymphocytic variant of hypereosinophilic syndrome [125]. It had been shown to be effective in lowering eosinophils and steroid doses as well as being well tolerated [124].

5.6.3.4 Anti-CD20
The depletion of B cells by rituximab, a monoclonal anti-CD20 antibody, which so far has been used for therapy of hematologic disorders, resulted in a rapid and sustained decrease of skin inflammation in AE patients, suggesting an important role B cells in the pathogenesis of AE [126]. Although IgE levels remained mainly unchanged, anti-CD20 treatment led to improvement of the skin lesions, implying that B cells play an important role in AE.

6. Potential future developments

6.1 Inhibition of chemokines
Many chemokines are involved in the recruitment of inflammatory cells in atopic diseases. Chemokines play an important role in orchestrating recruitment of leucocytes in inflammatory diseases [27] and, therefore, may represent a possible important target for anti-inflammatory therapies. Chemokines are important recruiters and activators of inflammatory cells and these infiltrating cells interact with resident cells, such as keratinocytes and fibroblasts, and may exert multiple biological actions through these pathways.

Over 50 chemokines are recognized so far activating > 20 different surface receptors. Chemokine receptors belong to the seven transmembrane receptor superfamilies of GPCRs. Some chemokines are selective for single chemokine receptors, whereas others are promiscuous and mediate the effects of several related chemokines. Chemokine receptors are assumed as possible therapeutic targets for inflammatory diseases such as asthma or AE.

CCR4 are selectively expressed on T_{H}2 cells and are activated by two chemokines, monocyte-derived chemokine and thymus- and activation-dependent chemokine (TARC). These chemokines are increased in affected skin as well as in serum of patients with AE and levels of TARC were proposed as suitable markers of disease activity of generalized AE patients. TARC/CCL17 is an important chemotactic factor
for the migration of T cells into the epidermis [127]. Therefore, it has been suggested that small molecule antagonists against CCR4 may prevent the migration of pathologically relevant skin-homing CLA plus memory T cells to the inflammatory cutaneous site.

The chemokine system is complex and about 50 ligands and 20 receptors are known so far, making a selection of appropriate specific antagonists difficult. Thus, another approach may be the development of broad spectrum chemokine inhibitors. The first broad spectrum chemokine inhibitor was investigated in a first human trial (Phase I trial, FX 125L) in 66 healthy volunteers and was tolerated well. Thus, broad spectrum chemokine inhibitors might be a novel approach to treat severe AE [128] or might even be developed for topical use in future.

Clinical trials are underway with therapeutics targeting chemokine pathways in other inflammatory diseases. It is hoped that the information generated from these studies will contribute towards our knowledge and be applied towards targeting severe AE.

6.2 NF-κB inhibition
Common drugs used in AE that inhibit calcineurin and act via inhibition of transcription factors are cyclosporine A, as a systemic agent, and tacrolimus and pimecrolimus, as topical agents. Another strategy would be the inhibition of NF-κB by other agents. This transcription factor regulates the expression of inflammatory cytokines, chemokines and proteases. Inhibitors of NF-κB kinase (IKK) 2 depress CXCR3 chemokines, which play a significant role in the inflammatory response in AE, suggesting potential complex interactions between signal transduction pathways [129].

IKK2 were tested in an animal model of asthma, an atopic disease with similar immunologic features. Although several IKK2 inhibitors are now in development, so far none has been tested in AE.

6.3 TLR agonists
TLR are involved in the microbial recognition by the immune system. Thus far, 10 members of TLR have been identified, which bind to microbial structures and ligands such as bacterial lipopolysaccharides, bacterial DNA and viral, double-stranded DNA. Some probiotics which are assumed to be effective in prevention of atopic diseases may function as they interact with TLRs.

TLRs activate signaling pathways with consecutive activation of NF-κB transcription factor and the MAPKs.

6.4 Antiproteases
There is evidence for an imbalance between proteases and antiproteases in impaired skin in AE. Polymorphonuclear and also eosinophil leukocytes are present in inflamed atopic skin and contain well-defined proteolytic enzymes in their granules. These can be released into tissues, producing a localized excess of proteases that causes a protease-antiprotease imbalance with subsequent tissue destruction.

This suggests that either inhibiting proteolytic enzymes or increasing the levels of antiproteases may be beneficial and theoretically should prevent the progression of the inflammatory response in AE. At present, for the treatment for asthma, nebulized inhibitors are in clinical development, and further work in this area is indicated to clarify any potential benefit either with systemic or topical use for patients with AE.

6.5 p38 MAPK inhibitors
Activation of protein kinases is a general mechanism of signal transduction in many cellular processes. Several intracellular signaling cascades have been characterized recently known as MAPK signaling cascades. MAPKs are expressed ubiquitously and regulate various responses depending on the cell type.

Several small molecule inhibitors p 38 MAPK have recently been developed. The four isofoms of p 38 MAPK regulate transcription by phosphorylation of transcription factors such as IL-8 and TNF-α [130]. Several inhibitors of p38 MAPK have now been developed as targets for anti-inflammatory therapy. One of them, the inhibitor of the p 38-α isoform, SD-282, inhibits the release of TNF-α by lung macrophages in vitro [131] as well as pulmonary macrophage recruitment in mice [132]. So far, publication is pending on how effective these molecules are in the anti-inflammatory treatment of AE.

6.6 Selective glucocorticoid receptor agonists or dissociated glucocorticoids
Because of the numerous adverse effects that can be seen by using glucocorticoids, research has focused on the development of improved glucocorticoids or GCR ligands. SEGRAs (selective glucocorticoid receptor agonists or dissociated glucocorticoids) could represent a novel future treatment option as recent studies have shown that SEGRAs compared to glucocorticoids have comparable anti-inflammatory and immunosuppressive but less adverse effects [133,134]. ZK 245186 was proven to be a potent anti-inflammatory compound and is currently investigated in clinical trials [135].

6.7 anti-IL-31
IL-31 is a cytokine that – if overexpressed – induces severe dermatitis in transgenic mice [136,137]. In patients who suffer from AE significantly higher serum levels of IL-31 could be detected compared to nonpruritic skin inflammation [136]. In human skin, IL-31 was mainly produced by CLA-positive T cells [138] and upregulated in patients with pruritic inflammatory diseases, especially in those with AE [139]. Further studies are required to investigate the role of IL-31 in AE and the role of IL-31 as a potential target for the treatment of eczema.

7. Expert opinion
To improve therapy in AE, we not only need novel drugs for treatment, but also better guidelines that are followed more closely by the patient and the medical community. Recently,
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guidelines for AE diagnosis and treatment based on literature review and repeated consenting group discussions have been established [41]. Finally, we have to work on the issue of patient adherence.

So far, corticosteroids are by far the most effective topical treatment for AE and part of their efficacy is due to inhibition of inflammatory cytokine expression. Tacrolimus and cyclosporin inhibit the transcription factor NFAT that regulates the secretion of different cytokines such as IL-2, IL-4, IL-5 and GM-CSF by T lymphocytes. The toxicity of cyclosporin limits its usefulness, when given orally. Tacrolimus and pimecrolimus have been successfully developed for topical use and their efficacy has been shown in many clinical trials.

Traditional systemic agents used for the treatment of AE are associated with significant potential side effects and often do not provide adequate therapeutic responses. Further development of new immunomodulating agents even for topical use of eczematous lesions should be encouraged. Choice of topical formulation is another important issue that will have to be addressed. In spite of the need for systemic therapy, the overall demand for topical therapies will remain high.

Despite multiple therapeutic modalities, treatment of AE with its chronic relapsing nature remains a challenge. Severe AE often cannot be adequately controlled with topical agents. Although remarkable therapeutic efforts have been achieved, patients suffering from the severe form of AE often remain refractory to topical treatment. The continuous use of current systemic therapies for AE is limited by end-organ toxicities.

The systemic treatment options to date (cyclosporine A, systemic glucocorticoids, azathioprine and mycophenolate mofetil) are limited in their applications and usually restricted to short-term use. Their use requires careful monitoring because of potential adverse effects (risk of myelosuppression, tumors and infections). Thus, novel therapeutic strategies with low side effect profiles are needed in the long-term treatment of these patients. Safe and effective topical and systemic therapy is greatly needed.

Biologic agents may offer distinct advantages over conventional pharmacotherapy in the treatment of AE. Biological agents have an immunomodulatory effect such as allergen immunotherapy. In general, in AE patients, biological agents were studied in clinical trials that included relatively small patient populations. Further studies with a larger patient population are warranted.

The immunologic pathways leading to atopic inflammation system are complex, making a selection of appropriate specific antagonists difficult. First trials with mAbs against single cytokines have shown diverging results. As the immune pathways that lead to AE are complex, it is likely that too selective anti-inflammatory or immunomodulatory agents might have limited effects. Because so many cytokines are involved in orchestrating and perpetuating inflammation in AE, development of a drug that inhibits the synthesis of multiple T helper 2-cytokines or chemokines may be a promising strategy to treat patients with severe AE. Thus, an approach may be the development of broad spectrum cytokine inhibitors or combination of different mAbs. Thus, these 'broad spectrum' biologicals might be a novel approach to treat severe atopic diseases and further immunomodulating agents might even be developed for topical use in future.

Research into new drugs for the treatment for atopic diseases may lead to the development of drugs with novel mechanism of actions and a refinement of the use of current drugs through modification of the molecular structure, new galenic systems and new combinations. Drugs with such novel mechanism of action may provide a therapeutic profile not seen with current drugs. Another approach is to manipulate the molecular structure of an existing therapeutic class (e.g., in a way that may improve the benefit:risks ratio). New delivery systems for existing drugs should be investigated, with the hope of improving tolerability, patient acceptance and adherence to therapy. Closer work between clinical academics and industry will be necessary to ensure that there is a rapid transfer of knowledge. The development of more effective and safer drugs will be an important goal for the future.

Acknowledgement

The authors thank B Aigner for assistance in the revision of the manuscript.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript. S Ploetz cooperates with the Aerztehaus Munich – Harlaching and is a consultant at the hospital of the ‘Barmherzige Brüder’, Munich, Germany. This work was supported by C Kuehne, Center for Allergy Research and Education (CK-CARE).
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