Topical therapy of atopic dermatitis with a focus on pimecrolimus

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Abstract

Atopic dermatitis (AD) is a chronic and relapsing, inflammatory skin disease characterized by impaired skin barrier function and immune system dysregulation that results in dryness, skin microbiome dysbiosis and intense pruritus. It is highly heterogeneous, and its management is demanding. Patients with AD are at greater risk of comorbidities such as attention-deficit hyperactivity disorder as well as other atopic diseases. Early-onset AD cases typically improve or resolve in late childhood; however, it is proposed that the prevalence of persistent or adult-onset AD is higher than previously thought. Basic therapy consists of emollient application and trigger avoidance, and when insufficient, topical corticosteroids (TCS) are the first-line treatment. However, corticophobia/steroid aversion and TCS side-effects, particularly on sensitive skin areas, lead to low compliance and insufficient disease control. Several long- and short-term randomized controlled and daily practice studies have demonstrated that topical calcineurin inhibitors, such as pimecrolimus, have similar anti-inflammatory effects to low-to-medium strength TCS, reduce pruritus and improve the quality of life of patients. In addition, pimecrolimus does not cause skin atrophy, is steroid-sparing and has a good safety profile, with no evidence for an increased risk of malignancies or skin infections. In general, pimecrolimus cream is well-accepted and well-tolerated, encouraging patient adherence and leading to its use by many physicians as a preferred therapy for children and sensitive skin areas.

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Conflicts of interest

Dr. Luger reports grants and personal fees from Meda Pharma S.p.A., a Viatris company, during the conduct of the study. Dr. Paller reports personal fees from AbbVie, Anaptysbio, Abeona, Almirall, Asana, Boehhringer-Ingelheim, Bridgebio, Dermavant, DermaSera, Eli Lilly, Exicure, Fore, Galderma, Incyte, Inmed, Janssen, LEO, Lifemax, Novartis, Pfizer, RAPT, Regeneron, Sanofi-Genzyme, Sol Gel and UCB, outside the submitted work. Dr. Irvine reports personal fees from AbbVie, Benovelent AI, LEO, Novartis, Regeneron and Sanofi, outside the submitted work. Dr. Sidbury reports grants from Brickle, Galderma and Regeneron, and a relationship with Micreos (no monies received), outside the submitted work. Dr. Eichenfield reports grants from Abbvie, personal fees from Almirall, Asana, Dermovant, Forte, Galderma, Incyte, LEO, Lilly, Regeneron, Sanofi-Genzyme and Novartis and grants and personal fees from Pfizer and Ortho Derm, outside the submitted work. Dr. Werfel reports personal fees from Meda Pharma S.p.A., a Viatris company, during the conduct of the study; grants and personal fees from AbbVie, LEO, Novartis and Pfizer, personal fees from Lilly and Sanofi and grants from Regeneron, outside the submitted work. Dr. Bieber was speaker and/or consultant and/or Investigator for AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Bayer Health, BioVerSys, Böhringer-Ingelheim, Bristol-Myers Squibb, Celgene, Daichi-Sankyo, Dermavant/Roivant, DermTreat, Domain Therapeutics, DS Pharma, RAPT/FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, IQVIA, Janssen, Kirin, Kymab, LEO, LG Chem, Lilly, L’Oréal, MenloTx,
Introduction

Definition, clinical appearance, classification, diagnosis

Atopic dermatitis (AD) is a chronic and relapsing, pruritic, inflammatory skin disease that is highly heterogeneous, with clinical appearance differing depending on age and severity. In infants, AD is usually acute, with lesions mainly on the face, cheeks and trunk, although not in the diaper area. Excoriations are common at this age. In toddlers and older children, the face, extensor surfaces of joints and flexures (e.g. the antecubital and popliteal fossae) are primarily affected. In adolescents and adults, often dry and lichenified plaques are present on hands, eyelids and flexures. In the head and neck subtype of AD, which may be associated with Malassezia species hypersensitivity, the upper trunk, shoulders and scalp can also be affected, although clinical presentation in adults is particularly variable. In addition to age-based heterogeneity in clinical characteristics, differences have been reported among patients with AD from different regions. For example, in contrast to European and American patients, an increase in markers of T helper cell (Th)17 activation has been shown in Asian patients, along with a predominance of the psoriasiform phenotype.

In the absence of specific diagnostic tests, various sets of clinical diagnostic criteria have been established for AD, including those from Hanifin and Rajka, the Japanese Dermatological Association, the UK Working Party’s Diagnostic Criteria for AD and the American Academy of Dermatology Consensus Criteria.

Epidemiology, prevalence, natural course

Atopic dermatitis has a worldwide prevalence of up to 20% in children and 3% in adults and is increasing, especially in developing countries. Prevalence has been reported to be higher in women than in men and the majority of patients (up to 60–80%) are thought to have mild disease. Environmental factors such as higher outdoor temperatures, water hardness, urban setting, pollution and smoking appear to be associated with an increased risk for AD.

The natural course of AD can be highly variable and numerous studies have provided sometimes conflicting information. In general, data suggest that up to 70% of early-onset cases greatly improve or resolve in late childhood, and severe early AD has been associated with prolonged disease (e.g. into adulthood). Based on longitudinal cohort studies and population-based estimates, it is proposed that the prevalence of persistent or adult-onset AD is higher than previously thought.

Previously, AD was considered the first expression of atopy [genetic predisposition to immunoglobulin (Ig)E sensitization] and the start of the so-called ‘atopic march’, which results in development of asthma and allergic rhinitis. Recently, epidemiological observations and molecular research have questioned the causative role of allergy in AD and demonstrated that epidermal and skin barrier defects are central to AD pathogenesis, along with immune system abnormalities. Food allergy/sensitization and inhalant allergens may, however, play an important role as a trigger of exacerbations in AD and the atopic march.

Burden of the disease – unmet needs

Atopic dermatitis considerably affects the quality of life and finances of patients and their families. Disease severity is directly correlated to decreased quality of life and increased costs, as a consequence of physical (itching, scratching, sleep disturbances, fatigue) and psychological (behavioural problems, irritability, crying, depression, anxiety, suicidal ideation) symptoms and the social (isolation, reduced self-esteem, bullying experience) impact of the condition.

Comorbidities

Children and adolescents with AD have a 1.5-fold increased risk for attention-deficit hyperactivity disorder; while further research is needed, mechanisms such as sleep deprivation and central nervous system exposure to inflammatory cytokines may underpin this association. Emerging data also suggest an increased risk for alopecia areata, rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes and some types of cancer.

Other possible comorbidities include manifestations of atopy, such as allergic rhinitis, asthma, food allergies, allergic conjunctivitis and eosinophilic esophagitis.

Pathophysiology

The debate around the pathophysiology of AD continues. Currently, skin barrier dysfunction and immune system dysregulation are considered to underpin AD pathophysiology, with genetic and environmental factors contributing to the development of disease. The inappropriate immune response in AD...
is dominated by T-cell infiltration and associated with IgE-mediated sensitization and neuroinflammation, which underlie pruritus, the cardinal symptom of AD.\(^1\) Skin microbiome dysbiosis, with *Staphylococcus aureus* colonization and increases during flares, is an additional disease characteristic.\(^1,29\)

**Genetics**

Epidemiological data support the heritability of AD.\(^1\) Null mutations in the gene encoding the epidermal protein filaggrin (FLG) give rise to the semi-dominant skin-scaling disorder ichthyosis vulgaris and represent the strongest known genetic risk factor for AD.\(^{1,30,31}\) These mutations reduce FLG expression, causing disruption of skin barrier function, which increases the risk of AD.\(^30\) Approximately 10% of individuals of European origin carry a single FLG mutation, may have signs of mild ichthyosis and are at an approximately three-fold increased risk of developing AD,\(^30\) with approximately 30% of patients with AD reported to be carriers of an FLG mutation.\(^32\) In contrast, more than 50% of FLG mutation carriers do not develop AD, demonstrating the complex nature of the disease.\(^30\) Association studies have identified more than 39 specific genomic regions that are likely to influence AD susceptibility.\(^33\) Many candidate genes appear to contribute to abnormalities of immune function, in particular to innate immune signalling, and T-cell activation and specification.\(^34\)

**Epidermal barrier dysfunction and cutaneous inflammation**

Impaired barrier function in AD can result in a number of characteristics, including increased transepidermal water loss, lower hydration, disturbed lamellar organization, increased skin pH and reduced expression of epidermal differentiation-related structural proteins (Table 1).\(^{35–43}\) These features contribute to the associated dryness and intense pruritus that characterize AD.\(^35–43\)

Even ‘unaffected’ skin in AD is not healthy skin. Unaffected skin presents with primary (from FLG loss-of-function mutations) and secondary (from type 2 inflammation) reduction of FLG, modified lipid structure and composition, and release of immune cytokines from keratinocytes.\(^{15,44}\) B- and T-cell priming are also observed in regional lymph nodes due to increased exposure to and uptake of antigens through the skin.\(^15\) Epidermal barrier challenges provoke the release of alarmins [interleukin (IL)-1\(\beta\), IL-25, IL-33 and thymic stromal lymphopoietin (TSLP)], which induce inflammation,\(^1\) characterized by a shift towards a type 2 immune response (Fig. 1).\(^{1,45}\) Inflammatory cell infiltration, mainly of CD4\(^+\) T helper cells (Th2 and Th22 cells in the acute phase, Th1 cells in the chronic phase of non-Black adults), and release of corresponding cytokines [IL-4, IL-5, IL-13, IL-31, interferon (IFN)-\(\gamma\)], contributes to the dysregulated immune response.\(^1,15,44\) Antigen-presenting cells are also increased, including several dendritic cell subsets, such as Langerhans cells.\(^36\)

In AD lesional skin, differential gene expression is observed.\(^47\) This primarily results from increased keratinocyte activity and T-cell infiltration, with a consequential upregulation of Th2, and to a lesser degree, Th22 and Th1 pathway cytokines.\(^1\) Langerhans cells and other dendritic cells react with allergens and antigens found in the damaged epidermis.\(^35\) Disruption of the skin barrier triggers keratinocytes to express thymus- and activation-regulated chemokines (TARC/CCL17) and macrophage-derived chemokines (MDC/CCL22), as well as IL-1\(\beta\), IL-33, and TSLP, which are all significant drivers of type 2 innate lymphoid cell (ILC2)- and Th2-cell-mediated immune responses.\(^1\)

**Dysbiosis – microbiome abnormalities**

Atopic dermatitis is characterized by an altered epidermal bacterial colonization pattern with greater abundance of *S. aureus*.\(^48\) There is a strong association between worsening disease severity and a reduction of skin bacterial diversity.\(^39\) *Staphylococcus aureus* has multiple effects on the pathogenesis of AD, including immune system activation, barrier breakdown, Th2 priming and induction of IgE and of eosinophils.\(^48–53\) Therapeutic manipulation of the microbiome, especially with commensals that kill *S. aureus*, might be one possible approach for the prevention or treatment of AD, but its impact on cutaneous or systemic immune activation, or epidermal barrier function, remains unclear.\(^54,55\)

**Neuroimmune interactions**

Dry skin and pruritus are the cardinal features of AD,\(^14,15,56\) with patients showing different pruritus activation patterns and kinetics compared with healthy volunteers.\(^57\) Various pruritogens are responsible, with signals transmitted via primary afferent neurons from the periphery to the central nervous system.\(^58\) The best studied pruritogen is histamine, which is released by mast cells, basophils and keratinocytes during type 1 allergic reactions.\(^1,58\) Nevertheless, other pruritogens such as endothelin-1 (ET-1) and TSLP, or Th2 cytokines such as IL-4, IL-13 and

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Table 1 Characteristics of the impaired barrier function in atopic dermatitis

| Characteristic                                      |
|----------------------------------------------------|
| Increased transepidermal water loss                |
| Lower hydration                                    |
| Diminished water-binding capacity                  |
| Decreased ceramide levels                          |
| Disturbed lamellar organization                     |
| Increased pH                                        |
| Diverging serine protease activity                 |
| Reduced expression of epidermal differentiation-related structural proteins |
| Increased permeability to low molecular chemicals  |
| Reduced skin microbiome diversity                  |
| Increased *Staphylococcus aureus* colonization      |
| Increased susceptibility to infection              |
| Increased nerve fibre density                       |

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IL-31, may be far more important than histamine for the induction and persistence of pruritus in AD, and may explain anti-histamines’ relatively low efficacy in treating AD-related pruritus. TSLP is released by keratinocytes and directly activates sensory neurons expressing transient receptor potential cation channel subfamily A member 1 (TRPA1). Although the Th2 cytokines IL-4 and IL-13 have been shown to directly sensitize afferent neurons via interaction with the IL-4 receptor subunit-α (IL-4Rα) and Janus kinase 1 (JAK1) in vitro, Oetjen et al. demonstrated that these cytokines do not function as acute pruritogens in vivo; rather, they potentiate stimulation by other pruritogens. IL-4 was shown to rapidly sensitize subsets of neurons to a variety of pruritogens and significantly amplified scratching behaviour to low doses of pruritogens including histamine. Potentiation of itch responses by IL-4/IL-13 explains the potent antipruritic responses to dupilumab, the anti-IL4R monoclonal antibody. IL-31 stimulates afferent neurons via IL-31Rα, transient receptor potential cation channel subfamily V member 1 (TRPV1) or TRPA1 subunits. The importance of IL-31 in pruritus is emphasized by its dramatic improvement within one week of initiation of the anti-IL-31Rα monoclonal antibody, nemolizumab, in patients with moderate-to-severe AD, although its effect on AD severity scores without concomitant TCS was limited.

Management of atopic dermatitis

The primary objectives of successful AD treatment are as follows: (i) restore epidermal barrier function; and (ii) counter chronic inflammation, decreasing pruritus, while improving quality of life. Optimal AD treatment also prevents relapses and prolongs remission.

Treatment algorithm

International AD treatment algorithms uniformly recommend stepwise therapy, adapted to disease severity. Thus, standard primary therapy universally treats the disturbed barrier function with emollients, includes short baths (5 min) and avoids trigger factors and stress. If emollient treatment is insufficient, guidelines recommend topical anti-inflammatory therapy (topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI)). Based on their long history of use, low cost and rapid mode of action, TCS are still considered first-line treatment for acute flares. Reactive treatment with low-strength TCS or TCI is recommended for acute flares in mild, transient AD (SCORing AD <25), whereas medium to high strength TCS is recommended for acute flares in moderate-to-severe AD (SCORAD >25). Successful management of AD requires an individualized approach and may include proactive treatment, which involves twice-weekly application of a medium strength TCS or a TCI 2–3 times per week to previously affected areas (now clear or almost clear), combined with liberal use of emollients on the whole body.

Short-term phototherapy (UVA-1, UVB, balneo-, phototherapy) may be used as an adjuvant therapy when topical medications are insufficient. If this option also fails or is untenable, systemic therapy is indicated. Systemic therapies include dupilumab as well as immunosuppressants such as cyclosporine, methotrexate, mycophenolate mofetil and azathioprine. Use of systemic corticosteroids is common, but is generally discouraged because of their side-effect profile and tendency for rebound shortly after discontinuation. Several new biologic agents and small molecule drugs are in development for the treatment of AD.

Topical anti-inflammatory therapy of atopic dermatitis

Topical corticosteroids

Topical corticosteroids act on immune cells, impeding antigen processing and inflammatory cytokine release. Furthermore, TCS reduce cell proliferation, neutrophil adhesion, human leukocyte antigen expression, chemotaxis, phagocytosis, collagen synthesis, capillary permeability and dilatation, while increasing lipocortin 1 production and protein catabolism. In addition to anti-inflammatory and immunomodulatory effects, TCS may also lead to local adverse effects, such as impairment of skin barrier function, development of striae and skin atrophy, perioral dermatitis, rosacea and allergic contact dermatitis, especially when not used properly. Systemic side-effects are rare, and occurrence is related to TCS potency, application site, TCS occlusion, percentage of body coverage and duration of use. TCS potency classification varies by location. In Europe, the most established classifications are those of the Anatomical Therapeutic Chemical/World Health Organization, British National Formulary and Niedner; all designate four potency groups from mild (group I) to very potent (group IV). The US system considers seven groups in reverse order. However, as potency is not solely responsible for the effects of TCS, the Therapeutic Index was introduced, which categorizes TCS based on the relationship of desirable vs. undesirable effects in AD.

Despite these tools for correct prescribing and the rarity of adverse effects when TCS are appropriately used, adherence to TCS treatment is low, with only 32% of patients reported to follow medical advice. Poor adherence may be due to TCSophobia/corticophobia, defined as exaggerated negative feelings and beliefs of patients and healthcare professionals about TCS, which can lead to insufficient AD control and increased healthcare costs.

Topical calcineurin inhibitors

In 2000, TCI became available as an alternative therapy to TCS. They exert anti-inflammatory effects by selectively inhibiting calcineurin-dependent T-cell activation, thereby reducing the expression of pro-inflammatory cytokines (Fig. 2). Two TCI are licensed, tacrolimus (0.03% and 0.1% ointments) and pimecrolimus (1% cream).

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In AD, defects in the epidermal barrier (Table 1) allow the increased penetration of antigens, which are detected by epidermal Langerhans cells and dermal dendritic cells. This leads to immune activation, characterized by the release of alarmins, B and T-cell priming and a shift towards a type 2 immune response, primarily involving Th2 and Th22 cells. The production of Th2 cytokines leads to IgE-class switching in B cells, which then activates eosinophils and mast cells. Mast cell-derived histamine and the Th2 cytokine IL-31 contribute to the sensation of pruritus. In response to barrier impairment, keratinocytes produce TSLP and IL-33, which interact with cutaneous sensory neurons to trigger pruritus induction. Th2 and Th22 cytokines also reduce the expression of barrier proteins. These changes form part of a negative cycle in AD skin, in which cutaneous inflammation and the ‘itch-scratch cycle’ further worsen epidermal barrier impairment. Defects in the epidermal barrier predispose AD skin to microbial dysbiosis and to S. aureus infections, which also damage the skin barrier. In chronic lesions, there is a shift away from a Th2 response towards a Th1 and Th17 response. AD, atopic dermatitis; AHR, aryl hydrocarbon receptor; cAMP, cyclic adenosine monophosphate; CRTH2, chemoattractant receptor homologous molecules expressed on TH2 lymphocytes; H4R, histamine receptor type 4; IgE, immunoglobulin E; IL, interleukin; PDE4, phosphodiesterase 4; Th, T-helper; S. aureus, Staphylococcus aureus; TRPA1, transient receptor potential cation channel, subfamily A, member 1; TRPV1, transient receptor potential cation channel subfamily V member 1; TSLP, thymic stromal lymphopoietin; ST2, serum stimulation 2.

Figure 1  Epidermal barrier dysfunction and cutaneous inflammation in AD (reprinted and adapted from J Allergy Clin Immunol, Vol 140, Issue 3, Paller A, et al., Therapeutic pipeline for atopic dermatitis: End of the drought? pp. 633–643, 2017, with permission from Elsevier). In AD, defects in the epidermal barrier (Table 1) allow the increased penetration of antigens, which are detected by epidermal Langerhans cells and dermal dendritic cells. This leads to immune activation, characterized by the release of alarmins, B and T-cell priming and a shift towards a type 2 immune response, primarily involving Th2 and Th22 cells. The production of Th2 cytokines leads to IgE-class switching in B cells, which then activates eosinophils and mast cells. Mast cell-derived histamine and the Th2 cytokine IL-31 contribute to the sensation of pruritus. In response to barrier impairment, keratinocytes produce TSLP and IL-33, which interact with cutaneous sensory neurons to trigger pruritus induction. Th2 and Th22 cytokines also reduce the expression of barrier proteins. These changes form part of a negative cycle in AD skin, in which cutaneous inflammation and the ‘itch-scratch cycle’ further worsen epidermal barrier impairment. Defects in the epidermal barrier predispose AD skin to microbial dysbiosis and to S. aureus infections, which also damage the skin barrier. In chronic lesions, there is a shift away from a Th2 response towards a Th1 and Th17 response. AD, atopic dermatitis; AHR, aryl hydrocarbon receptor; cAMP, cyclic adenosine monophosphate; CRTH2, chemoattractant receptor homologous molecules expressed on TH2 lymphocytes; H4R, histamine receptor type 4; IgE, immunoglobulin E; IL, interleukin; PDE4, phosphodiesterase 4; Th, T-helper; S. aureus, Staphylococcus aureus; TRPA1, transient receptor potential cation channel, subfamily A, member 1; TRPV1, transient receptor potential cation channel subfamily V member 1; TSLP, thymic stromal lymphopoietin; ST2, serum stimulation 2.
Although their principal mode of action is similar, they have distinct pharmacological profiles. 

Experimental studies with porcine skin suggest that the high lipophilicity of pimecrolimus leads to low in vivo percutaneous absorption. 

Meta-analyses of randomized controlled trials demonstrate that both tacrolimus and pimecrolimus are effective and well tolerated in the treatment of AD. 

In 2005, the US Food and Drug Administration (FDA) issued a black box warning relating to a possible increased lymphoma risk with tacrolimus and pimecrolimus. 

Topical calcineurin inhibitors (TCIs) bind with high affinity to macrophilin-12 (FKBP-12), forming a complex which inhibits the activity of the calcium-dependent phosphatase, calcineurin. 

Calcineurin dephosphorylates and induces a group of transcription factors, NFATs, which facilitate the transcription of IL-2. 

By impeding this process, TCIs inhibit IL-2 production and the resulting synthesis of other Th2 pathway cytokines. 

TCIs therefore inhibit the proliferation and activation of T cells, and differentiation into the Th2 subtype. 

TCIs also act in mast cells to inhibit the production of TNF-α and the release of pro-inflammatory mediators, such as histamine and tryptase. 

Unlike corticosteroids, TCIs are selective in their action and primarily affect T cells and mast cells. 

CaN, calcineurin; IL, interleukin; MP-12, macrophilin-12; NFAT, nuclear factor of activated T cells; TCI, topical calcineurin inhibitor; Th, T-helper; TNF-α, tumor necrosis factor alpha.
Clinical trials with pimecrolimus in infants, children and adults  Many controlled clinical studies and those reflecting clinical practice have demonstrated the efficacy and safety of pimecrolimus. A 6-month, open-label, multicentre study in 947 patients aged ≥3 months with AD of all severities investigated the safety and efficacy of pimecrolimus. At week 24, 64% of infants and 65% of children with severe/very severe facial disease at baseline were clear/almost clear of AD on their face. Patients aged <18 years saw most improvement in signs of AD within the first week of treatment, compared with adults, who saw gradual symptom improvement throughout the treatment course. Findings in infants, as reported by Kapp et al., were similar. In patients with head and neck dermatitis intolerant of, or dependent on TCS, twice-daily application of pimecrolimus for six weeks improved facial symptoms vs. vehicle (47% vs. 16%; P < 0.001) and reversed skin thinning (Fig. 3a). Eyelid dermatitis responded equally well to pimecrolimus treatment (45% clearance vs. 19% with vehicle; P < 0.001). Aschoff et al. observed that TCS and not pimecrolimus led to significant but transient epidermal thinning after just two weeks of twice-daily application on unwrinkled forehead skin of 20 adults with mild-to-moderate AD (Fig. 3b). Both of these studies demonstrate the suitability of pimecrolimus for skin areas sensitive to atrophy and telangiectasia from TCS. Furthermore, in children with severe and very severe AD, pimecrolimus had a significant steroid-sparing effect compared with vehicle. Patients receiving pimecrolimus required steroids on 29% of study days compared with 35% for patients on vehicle (P = 0.1841). This benefit was more pronounced in the head and neck of patients with acute severe disease, where steroids were used on 10% of study days with pimecrolimus vs. 30% with vehicle (P < 0.0001). Occlusion did not change the absorption or safety profile of pimecrolimus in children, adolescents or adults, possibly due to its lipophilicity.

The safety and efficacy of pimecrolimus were also demonstrated in a 5-year study (Petite study) in infants (≥3 to <12 months of age) with mild-to-moderate AD. Pimecrolimus did not affect the immune system and was steroid-sparing, and no cases of lymphoma were observed.

Furthermore, the Study of the Atopic March investigated whether early intervention with pimecrolimus was able to restrict the atopic march in 1091 infants aged 3–18 months with recent-onset AD and also to evaluate the efficacy and safety of pimecrolimus vs. vehicle. Rescue therapy with fluticasone propionate 0.05% cream was permitted if there were no signs of improvement after 3 days of study medication. Although no significant difference between the pimecrolimus- and vehicle-treated groups was found in the development of atopic comorbidities, pimecrolimus was significantly more effective than vehicle in the treatment of AD at Week 14. In addition, the safety profile of pimecrolimus was similar to vehicle, with most adverse events mild in nature in the two treatment groups. In 71 children with moderate AD receiving pimecrolimus 1% cream, the ease of application was rated as ‘excellent’ or ‘very good’ by 76% of patients/caregivers.

Overall, pimecrolimus is steroid-sparing and reduces the number of disease flares (Fig. 3c) and the overall burden of mild-to-moderate AD (Fig. 3d). Thus, patients are less dependent on topical steroids and have no risk of skin atrophy.

Therapy of sensitive skin areas with pimecrolimus Sensitive skin is defined by the International Forum for the Study of Itch (IFSI) as ‘A syndrome defined by the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli that normally should not provoke such sensations. These unpleasant sensations cannot be explained by lesions attributable to any skin disease. The skin can appear normal or be accompanied by erythema. Sensitive skin can affect all body locations, especially the face’. Sensitive skin may be related to AD, but epidemiological data are not clear. The pathophysiology of sensitive skin may be similar to neuropathic pruritus in the context of small fibre neuropathy. In contrast to ‘sensitive skin areas’ (eyelids and other parts of the face, neck, genital area, axilla, skin flexures), which have a thinner epidermal layer, skin sensitivity is not associated with a change in epidermal thickness.

Sensitive skin areas are the first to express AD in infants and are more vulnerable to penetration of irritants and allergens, as well as thinning following the application of TCS. Therefore, TCI are preferred by current guidelines for the long-term management of sensitive skin areas, because they do not induce skin atrophy. Also, relative to TCS, TCI have generally been reported to maintain and/or result in slight reductions or increases in the expression of skin barrier proteins, with a tendency towards increased expression of FLG demonstrated with pimecrolimus, suggesting a role in epidermal repair.

Effect of pimecrolimus on pruritus Pruritus is known to damage the skin barrier in AD and to increase inflammation, which further provokes pruritus, and leads to the ‘itch-scratch’ cycle. Pruritus affects the quality of life of patients and their caregivers considerably. Therefore, antipruritic therapy and suppression of the itch-scratch cycle are essential for successful treatment of AD.

Pimecrolimus mediates antipruritic effects by inhibition of cutaneous T-cell activation and proliferation, supporting skin barrier repair, and by suppression of inflammatory cytokine synthesis (Th1- and Th2-type cytokines, including IL-13). Pimecrolimus may also reduce pruritus via desensitization of TRPV1 receptor-expressing cutaneous nerve fibres, and inhibition of the release of substance P (SP), a major mediator of pruritus in inflammatory skin lesions. Clinical
studies demonstrated that targeting SP with neurokinin 1 receptor (NK1R) antagonists such as aprepitant or serlopitant had significant antipruritic effects compared with baseline and/or placebo in patients with chronic pruritus, including those with atopic diathesis, AD or prurigo nodularis.144

A meta-analysis of 42 randomized controlled studies in AD evaluated the antipruritic effect of topical therapies (16 studies with pimecrolimus, six with tacrolimus, six with TCS, and four with topical antihistamines).147 Risk of pruritus was reduced by 36% with TCI, 34% with TCS and 27% with topical antihistamines, in comparison with corresponding vehicles.147 In adult patients (n = 192) with moderate-to-severe AD, significant reduction in pruritus was observed within 48 h of pimecrolimus treatment, while in the vehicle group pruritus worsened.148 In a study of 198 adults with mild-to-moderate AD and moderate/severe pruritus, pimecrolimus treatment led to improvement of pruritus within 48 h in more than half (56%) of patients vs. 34% in patients who received vehicle (P = 0.003).149 The antipruritic effect of pimecrolimus was also demonstrated in studies that reflect daily practice, including over 10 000 patients with AD.109–111

Quality of life and pimecrolimus Several studies, including analysis of data from the 2007 National Survey of Children’s Health in the United States, demonstrated that patients with AD suffer from substantial physical and psychological burden, affecting the patient’s and their family’s quality of life.26,150,151

Several short- and long-term studies have confirmed that pimecrolimus significantly improves the quality of life of adults and children with AD and their families compared with control-
Long-term management of atopic dermatitis: flare prevention

Pimecrolimus also demonstrated efficacy in the long-term management of moderate AD and relief of early signs/symptoms of disease.125 Patients in the control group were twice as likely to experience flares (defined as an Investigator’s Global Assessment score of 4 or 5 with requirement for second-line corticosteroid therapy) by 6 or 12 months compared with the pimecrolimus group, regardless of baseline disease severity.125 In addition, more patients in the control group required additional TCS therapy (62.9% vs. 35% at 6 months; 68.4% vs. 42.6% at 12 months).125 Similarly, in a long-term, randomized, vehicle-controlled study with patients with a history of mild-to-moderate AD (n = 543), treatment with pimecrolimus vs. vehicle at the first signs/symptoms of relapse significantly reduced the mean number of flares (worsening of disease requiring treatment with TCS) from 1.39 to 0.97 (P = 0.0014).126 Moreover, the number of TCS-free days was significantly greater (P < 0.001) in the pimecrolimus group (152 days) vs. the vehicle group (138.7 days).126 However, in atopic hand dermatitis, such results, as assessed by number of patients in stable remission, could not be confirmed.155 In the long-term management of facial mild-to-moderate AD, half of pimecrolimus-treated children and adolescents had no flares (defined as unacceptable severity of itching/scratching or onset of oozing, not controlled by study medication) on their faces compared with 37.5% (P = 0.012) of vehicle-treated patients.154 Also, the need for pimecrolimus therapy has been reported to decrease over time, indicating a lasting effect on disease control with reduced disease burden.155

Therapy adherence to pimecrolimus. Because AD persists in up to 60% of patients,156 lifelong skin care is often required. Therefore, besides good efficacy, the safety, tolerability and acceptance of topicaly applied products are often important for consistent adherence to the treatment.

Corticophobia, also termed steroid hesitancy, often leads to reduced adherence to TCS therapy and lack of treatment success.157 In several studies, over 70% of patients and their parents reported being worried about using TCS.152,157,158 In contrast, in a study with 3200 patients with AD, approximately 60% were not concerned about using pimecrolimus cream on sensitive skin (face, neck or flexures) vs. 10% with TCS; almost 93% of patients who received pimecrolimus agreed that therapy was well tolerated vs. <40% of patients who received TCS, and 80% felt optimistic with pimecrolimus, as opposed to 24% with TCS.152 Additionally, more than twice as many patients who received pimecrolimus, vs. those who received TCS, felt that it was easy to apply.152

Pimecrolimus - Safety and adverse events

Infections
The skin of patients with AD shows enhanced susceptibility to bacterial and viral infections.159 In particular, S. aureus constitutes 90% of the bacterial microflora on lesional skin and may also colonize normal appearing skin.160-162 Herpes simplex virus and Malassezia sympodialis infections occur as well.5,163

In a 1-year, double-blind, clinical study of pimecrolimus in comparison with conventional AD treatment (regular use of emollients for daily skin care and short-term use of moderate potency corticosteroids for flares), no between-group differences were recorded in time to first occurrence of bacterial skin infection or in incidence of individual bacterial skin infections.155 Although there were no between-group differences in the incidence of individual viral skin infections, the incidence of all (grouped) viral skin infections was higher in the pimecrolimus group vs. the conventional treatment group (12.4% vs. 6.3%; P = 0.038).125 In contrast, another study found that twice as many TCS-treated vs. pimecrolimus-treated patients with AD had skin infections.164 In the same population, total bacterial infections, folliculitis and herpes simplex infections were also significantly less frequent in the pimecrolimus group compared with the TCS group.164 In a review of the combined results of 10 studies (four pharmacokinetic studies and six clinical trials) conducted in 1133 infants with mild-to-severe AD, the incidence of total bacterial, fungal, parasitic and viral skin infections during double-blind studies or double-blind phases of studies was comparable for patients treated with pimecrolimus and vehicle-treated patients.165 Low incidence of skin infections with pimecrolimus was also confirmed by a 6-month open-label study conducted in daily practice with 947 patients aged ≥3 months and by a 15-week daily practice study in 3502 adult patients with AD.109,111 Likewise, the 5-year Petite study of Sigurgeirsson et al.122 in infants with mild-to-moderate AD observed similar skin infection rates in the pimecrolimus and TCS treatment groups. In a systematic review of long-term (≥12 weeks) clinical studies of treatment with TCS or TCI in patients aged <12 years with AD, incidence of skin infections was generally low in pimecrolimus-treated children and similar to that reported in vehicle-treated children.115
Effect of pimecrolimus on the immune system
After topical application, pimecrolimus is more specific in its actions than TCS, inhibiting transcription and release of inflammatory mediators from T cells without affecting dendritic cells. Additionally, treatment with pimecrolimus caused a smaller reduction in the levels of active antimicrobial peptides (human beta-defensins and cathelicidin) than treatment with TCS. This selectivity may explain the lower susceptibility for skin infections observed in pimecrolimus- vs. TCS-treated patients.

Moreover, low systemic absorption explains the absence of systemic immune effects following topical application of pimecrolimus. This is consistent with the generation of normal antibody titres to common vaccine antigens, observed in a study of 2418 pimecrolimus or TCS-treated infants with AD, and in a review of the combined results from six clinical trials in 1098 infants with mild-to-severe AD treated with pimecrolimus for up to 2 years.

Lymphoma and skin cancer
The application of TCI is associated with perceived safety concerns due to the boxed warning issued based on a theoretical increased risk of lymphoma and non-melanoma skin cancer associated with systemic administration of tacrolimus, despite lack of evidence of systemic absorption of topical tacrolimus or pimecrolimus.

A large retrospective observational study found that the topical use of pimecrolimus and tacrolimus is associated with a small excess risk of lymphoma in individual patients. However, this finding could be due to confounding by severity of AD, increased monitoring of severe patients and reverse causation. AD severity is known to be a significant risk factor for the development of lymphoma. A systematic review and meta-analysis found that the risk of lymphoma is increased in cohort studies but not in case–control studies and that TCI and TCS do not appear to contribute significantly to the overall risk. For example, in a cohort study which evaluated 121 289 person-years of follow-up contributed by 92 585 pimecrolimus initiators, incidence of lymphoma was found to be similar among pimecrolimus, tacrolimus and TCS users, with the risk of lymphoma higher in all three treatment groups compared with the general population. In contrast, Arellano et al. found no association between pimecrolimus use and risk of lymphoma in patients with AD. Another longitudinal cohort study, based on over 25 000 person-years of follow-up, also concluded that it is unlikely that topical pimecrolimus increases the risk of malignancy. Calculations of data from clinical registries, such as the clinical registries, such as the Mycology Registry of North America, suggest that the risk of lymphoma is similar among TCI and TCS users, with the risk of lymphoma higher in all three treatment groups compared with the general population.

In summary, the current black box warning is based on theoretical lymphoma risk and restrictions regarding TCI use in children are no longer justified. The safety and efficacy of pimecrolimus have been demonstrated in phase 3 trials with over 25 000 person-years of follow-up, also concluding that it is unlikely that topical pimecrolimus increases the risk of malignancy. In conclusion, the risk of lymphoma is similar among TCI and TCS users, with the risk of lymphoma higher in all three treatment groups compared with the general population.

Summary and conclusions
Atopic dermatitis is a common, inflammatory skin disorder affecting the quality of life of patients and their caregivers. Ideally, therapy should improve dermatitis and accompanying pruritus, as well as prevent flares. Applied topical treatments should be effective, well-tolerated and support patient adherence. TCI (pimecrolimus and tacrolimus) fulfill these expectations. The safety and efficacy of pimecrolimus have been demonstrated in the treatment of flares and as a maintenance therapy in mild-to-moderate AD, particularly in sensitive skin areas such as the face, eyelids and skin folds.

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