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ATOPY

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EDITO

Stéphane FAUVERGHE
NAOS International Medical Relations Director

Dear All,

I am very pleased to present you the 1st edition of Bioderma Updates Series dedicated to Atopy.

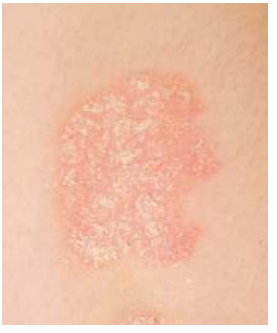
Since 2020, BIODERMA is regularly organizing International e-symposia dedicated to Dermatology, for dermatologists and all health care professionals interested in Dermatology, with always high-level updates on skin disorders presented by renowned experts in their field.

*In this 1st publication, you will find the summary of the recent e-symposium on **Atopy : Highlights & New Insights**, with Prof. Carsten FLOHR from UK, Prof. Laurent MISERY from France and Dr. Sandy SKOTNICKI from Canada as speakers.*

During this e-symposium, Carsten FLOHR presented new data on systemic treatments for children suffering from atopy, Laurent MISERY delivered an update on itching and finally Sandy SKOTNICKI presented the role of skin care in the management of atopy & its impact on the skin barrier.

I wish you all an enjoyable, enriching and interesting reading.

SUMMARY



SPEAKERS'S SHORT BIOGRAPHIES

Carsten FLOHR

United Kingdom

Professor Carsten FLOHR holds the Chair in Dermatology and Population Health Science at St John's Institute of Dermatology, King's College London, where he directs the Unit for Population-Based Dermatology Research.

He studied at Cambridge and Oxford Universities and then trained in both Paediatrics and Dermatology.

Carsten FLOHR was the first UK National Institute for Health Research (NIHR) Clinician Scientist in Dermatology (2009-2014) and the only dermatologist awarded a Career Development Fellowship from the NIHR (2014-2019).

He has a particular interest in novel methods of atopic dermatitis (AD) prevention (early life risk factors) and therapeutics, especially in severe AD.

He is Chief Investigator of the UK-Irish TREatment of severe eczema in children Trial (TREAT), which compares cyclosporine with methotrexate in children with recalcitrant atopic eczema. He is also Chief Investigator of the Softened water for eczema prevention trial (SOFTER) and the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR), as well as the EU-funded BIOMAP and Trans-Foods consortia.

Prof. FLOHR is a Founding Director of the International Eczema Council and Past President of the British Society of Paediatric Dermatology, as well as an Honorary Member of the Société Française de Dermatologie.

He is also Founding Editor of the Evidence-Based Dermatology Section of the British Journal of Dermatology and the Clinical Trials Editor of the F1000 Atopic Dermatitis Section.

Laurent MISERY

France

After studies and his first professional years in Lyon and Saint Etienne, Laurent MISERY became professor of Dermatology at the University of Brest.

He is now head of the department of Dermatology at the University Hospital of Brest.

Laurent MISERY founded and is the director of the Laboratory on Interactions Neurons-Keratinocytes (LINK) and the French Expert Centre on Itch. His team is dedicated to translational research on itch, from fundamental (biological and physiological) to pathophysiological, clinical, psychological and therapeutic aspects.

He is especially interested in the relationship between skin and the nervous system, from the biological point of view (co-cultures between skin cells and neurons) to the clinical (pruritus, sensitive skin) or psychological points of view.

Prof. MISERY is chairman of the EADV task force of psychodermatology.

His research interest is : sensitive skin; skin irritation; irritant; sensitivity; skincare products.

He was distinguished with the Herman Musaph Award in 2017.

Sandy SKOTNICKI

Canada

Dr. Sandy SKOTNICKI is the founding director of the Bay Dermatology Centre and is Assistant Professor at the University of Toronto, Department of Medicine in the Divisions of Dermatology and Occupational and Environmental Health. Dr. SKOTNICKI started the Bay Dermatology Centre in 2006 in an effort to provide a full-service Dermatology centre that focuses on the patient, not procedures.

She is a Diplomat of the American Board of Dermatology, and a member of the Canadian Medical Association, Canadian Dermatology Association, American Dermatology Association and American Contact Dermatitis Society.

Dr. SKOTNICKI is a consultant Dermatologist at St. Michael's Hospital in Toronto and is an expert in Allergic Skin Disease. She is also a consultant for the Workplace Safety Insurance Board.

Active in research and education, Dr. SKOTNICKI has been teaching University of Toronto Dermatology, Allergy and Family Medicine residents at her St. Michael's Hospital clinic since 1999. She is also a member of the Centre for Research Expertise in Occupational Disease & has published numerous articles on different aspects of Allergic Skin Disease.

Widely regarded as the "go to" Dermatologist in Canada for ingredient reactions and safety, she regularly provides commentary and contributes to medical journals, media outlets and speaks on reactions to chemicals in the skin-care industry.

COMPLEX PEDIATRIC ATOPIC DERMATITIS: A SPOTLIGHT ON SYSTEMIC THERAPIES

CARSTEN FLOHR

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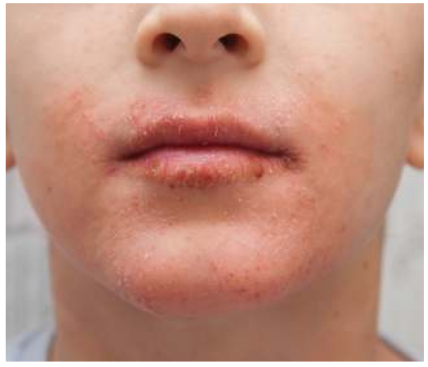
Guy's & St Thomas' NHS Foundation Trust, King's College, *London, UK*



While nowadays the therapeutic revolution in systemic therapies in atopic dermatitis (AD) is impressive, it still mainly focuses on adults, while pediatric trials are commonly performed once studies in adults have been completed. With several novel systemic treatments having been marketed, new therapeutic options are more and more frequently available for the pediatric population.

This article provides some information about conventional as well as novel treatment options in AD, along with an explanation of their targets within the complex inflammatory pathways in AD. Moreover, it provides three cases of severe pediatric eczema and how these cases were managed.

Based on the enhanced understanding of the immunological pathways in AD, a large number of therapeutic targets have now been identified. These include cytokines, such as Interleukin (IL)-33 targeted by Lebrikizumab, the cytokine thymic stromal lymphopoietin (TSLP) targeted by Tralokinumab and the Th2 signaling pathway targeted by Dupilumab.[1-4]

Dupilumab, the most frequently used biologic, is a human monoclonal antibody directed against the IL-4Rα subunit of the IL-4 and IL-13 receptors.[5, 6] A clinical study with Dupilumab conducted in children aged between 6 and 11 years provided similar results to those in adolescents with uncontrolled moderate to severe AD.[7, 8] It was overall well tolerated, even though cases of eosinophilia and conjunctivitis were reported.[9, 10] Conversely, blocking IL-5, IL-22 and IL-23 signaling has not yielded much promise for AD and pediatric study results for Nemolizumab, targeting the itch-mediating cytokine IL-31 are lacking.[11] Selective JAK inhibitors, which are broader in their anti-inflammatory effect, are eagerly awaited, while data on Omalizumab in pediatric AD has not shown improvement at the level of a minimal clinically important difference (MCID) in disease severity.[12]

To date, Cyclosporine A remains the only conventional systemic that is licensed in AD patients aged above 16 years, one of main reasons why it is still widely prescribed.[19]

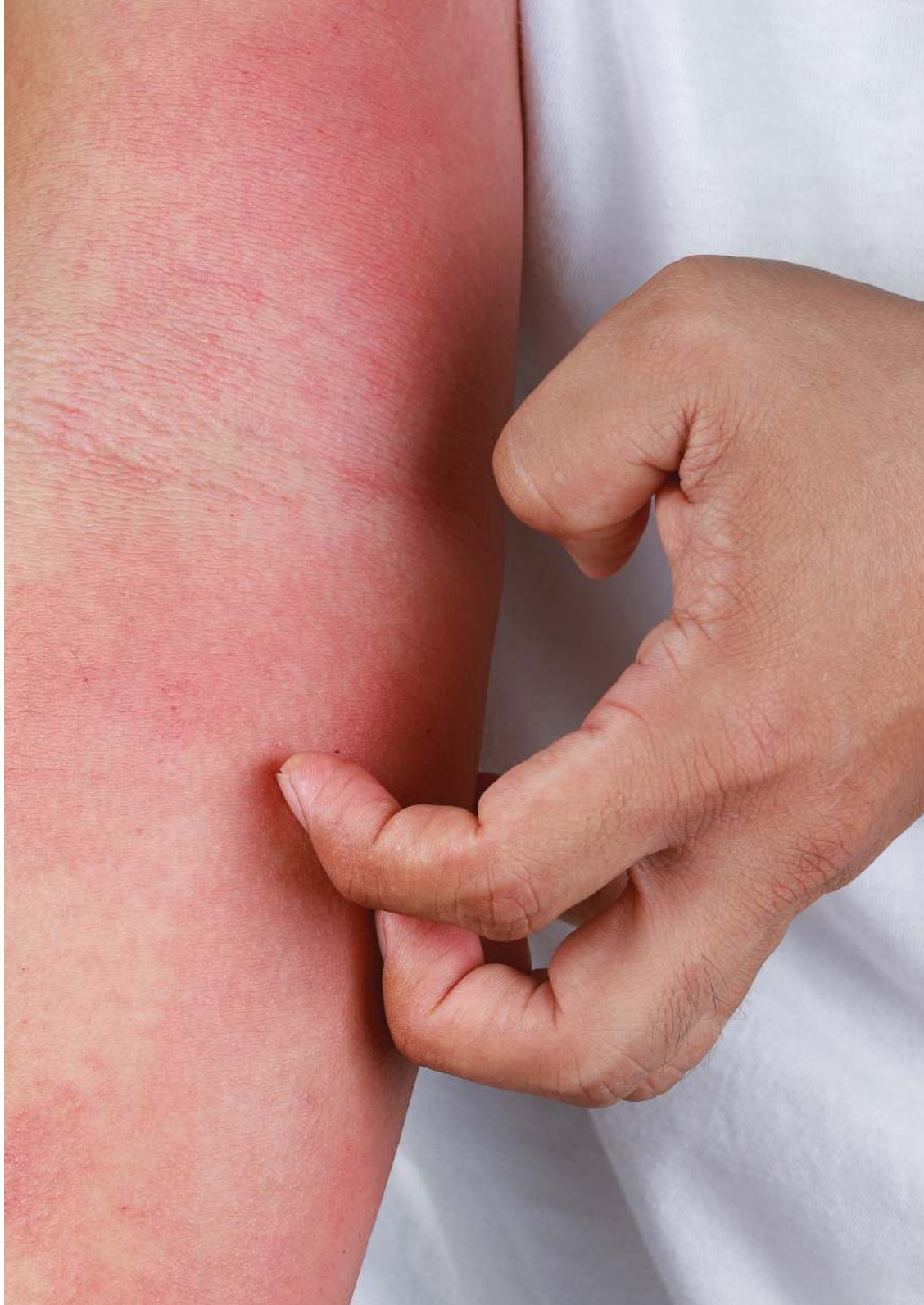
Overall, there is only a small amount of data about the use of systemic medications in pediatric AD populations available, mainly case series and case-control studies. Where pediatric data are available from clinical trials, the assessed treatments are often not commonly used, if at all. Moreover, it is frequent that pediatric patient data is not separately reported in clinical studies.[19-26]

Currently, there is only one published paediatric AD clinical trial that has assessed the efficacy of Methotrexate and Cyclosporine A, suggesting that both treatments work equally well with a SCORAD reduction just under 50 % after 24 weeks. Both drugs were well tolerated.[27] However, the study was small (20 participants per study arm) and therefore statistically underpowered, and the agents under-dosed; 2.5 mg/kg/day for Cyclosporin A and a fixed dose of 7.5 mg per week for Methotrexate.

Conversely, in the UK and many other settings where licensing considerations are not important, Methotrexate has emerged as the 1st line conventional systemic for AD in most departments. However, as for all immunosuppressive drugs, it bears safety concerns and long-term safety data from AD cohorts are currently missing.[28] Interestingly, latest research indicates that Methotrexate works as a selective Janus kinase inhibitor.[29]

Known side effects of Methotrexate include nausea, liver disturbance, and, rarely, bone marrow suppression. However, it is generally considered safe during long-term administration for paediatric patients. Its relatively slow onset of action and, while there is no clinical evidence, it is supposed to have the potential to induce long-term remission.[30]

Therefore, treating severe AD should consist of much more than starting a systemic medication. AD is a multifactorial and complex disease, driven by the vicious itch-scratch cycle. Itching can cause profound sleep disruption and many patients suffer from psychological and psychiatric comorbidities.[31] Scratching frequently causes skin infections, contributing to disease flares and chronicity, and many patients also report concomitant food and respiratory allergies that feed into the disease process.[32] For this reason, treating severe AD should always be a team approach. Ideally, a multidisciplinary team that includes pediatric dermatologists, clinical nurse specialists, pediatric allergists and clinical psychologists, pediatric respiratory medicine, and , where available, a research team to provide access to new therapeutics all help to treat severe pediatric AD in a holistic way.



In the following paragraphs, three cases of children with severe AD who were treated in our clinic are presented.

CASE N°1

The 1st case reported the treatment journey of an 8 year-old boy with severe AD since early life; who also suffered from hay fever and asthma. He was dependent on potent topical steroids and oral prednisolone, suffered from recurrent infective exacerbations and had several hospital admissions for this. Moreover, due to frequent safety blood taking, he had developed a profound needle phobia. His AD worsened with phototherapy and he developed high blood pressure and renal impairment on Cyclosporin A. Despite adequate metabolite levels, he was non-respondent to Azathioprine, Methotrexate and Mycophenolate Moletil. He then successfully received Dupilumab in compassionate use, with a remarkable treatment outcome, even after 10 months of continued use.

CASE N°2

The 2nd case concerned a 10-year old girl in whom all conventional treatments had failed. She received Mycophenolate mofetil (after having been unsuccessfully treated with Cyclospirin A and Methotrexate) as well as prophylactic oral antibiotics for her recurrent bacterial skin infections, with an insufficient treatment outcome. She then received Dupilumab at 200mg, leading to a cleared AD after six weeks. However, after about four months into Dupilumab therapy she developed yet another severe infection-driven flare, and her AD did not settle down sufficiently, once the skin infection had been adequately treated. Methotrexate was subsequently added in to the Dupilumab, but this did not result in adequate disease control either. She has now been switched to Abrocitinib with a good treatment effect.

Unfortunately, she has already had several episodes of herpes simplex infections since starting the medication, requiring Valaciclovir prophylaxis.

CASE N°3

The 3rd case concerned a 10-year old girl with a lifelong, severe AD, brittle asthma, severe hay-fever and many allergies, and who failed on all conventional treatments. She could not participate in any clinical trial, for instance with Baricitinib, as she required oral Prednisolone and hospital admission when undergoing the washout period.

Based on the above described evidence and on the experiences observed in his clinic, Carsten FLOHR considers that further novel treatments are urgently needed to treat pediatric AD. Moreover, head-to-head studies between conventional and novel treatments, as well as between conventional and between novel treatments, should be performed to directly assess the clinical efficacy of the different systemic AD treatments, thus allowing for a ranking in efficacy. In the meantime, network meta-analyses allow multiple comparisons of treatments in a unified analysis, including not only direct head-to-head study data but also indirect treatment comparisons from placebo-controlled trials.[33, 34] An update of Drucker *et al.* on this issue has been published in 2020.[35]

Moreover, treatment registries will be helpful vehicles to assess the long-term treatment effectiveness and safety of both novel and conventional systemic medications, also because many patients are excluded from participation in clinical trials due to rather strict inclusion criteria.

To this end, the UK-Irish A-STAR and other national AD systemic treatment registries provide 'real world' data on the more long-term treatment effectiveness and safety for systemic atopic eczema medication, comparing conventional and novel agents. Some registries also include a health economic assessment and a bioresource for molecular and stratification studies.

KEY MESSAGES

- Conventional systemic treatments remain the standard first line treatments for severe pediatric AD in most countries
- Of those, methotrexate (0.4 mg/kg/week) is now increasingly used
- Cyclosporin A at 4-5 mg/kg/day may be indicated for a faster onset of action, but data from an adequately powered RCT comparing Cyclosporin A with Methotrexate is currently lacking
- Dupilumab is now licensed for children from 6 years of age
- JAK inhibitors (Abrocitinib and Upadacitinib) are promising new therapies, even in those patients who failed treatment with Dupilumab
- Treatment registries to assess the long-term treatment effectiveness and safety are needed, as well as more head-to-head (rather than placebo-controlled)
- Network meta-analyses allow us to compare the efficacy of the different conventional and novel therapies, even if most of the evidence comes from placebo-controlled trials

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ATOPIC DERMATITIS: BEHIND THE ITCH

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Atopic dermatitis (AD), a chronic relapsing inflammatory skin condition, has a wide-ranging impact on patient quality of life. AD is caused by a complex interaction between immune dysregulation, epidermal gene mutations, and environmental factors which disrupt the epidermis, causing intensely pruritic skin lesions. Chronic pruritus (itch) constitutes a heavy burden, with almost a third of the patients in one European study reporting the itch as awful, and half of them as refractory.[1]

Itch, the main symptom in AD, is a challenging issue. Skin lesion distribution is heterogeneous, with on- and outside-lesions.[2] It has a substantial impact on sleep, cognition, appearance (scratching movements and lesions), psychological well-being, quality of life, sexual life, etc. Until now, its mechanism of action has been poorly understood, and the effects of treatment have been disappointing. Itching can be exacerbated by various factors including skin dryness, heat, sweat, contagious itch, anxiety, depression, and stress. In addition, woolen clothes, scratching (itch-scratch cycle), irregular habits, insomnia, nocturnal behaviour, and inflammation can also exacerbate itching.[3]

Itch is caused by a complex interface between skin, keratinocytes, cutaneous nerve fibers, pruritogenic molecules, and the peripheral and central nervous systems. The itch sensation emanates from the activation of nerve endings around the dermo-epidermal junction.[4] These nerve fibers belong to a specialized class of itch-provoking neurons ("pruriceptors") and are characterized by a highly focal spatial activation pattern.[5] Identification of the specific or selective itch receptors in the skin was a major discovery.[6] Itch-mediating primary sensory neurons are equipped with distinct receptors and ion channels for itch transduction, including Mas-related G protein-coupled receptors (Mrgprs), protease-activated receptors, histamine receptors, bile acid receptor, toll-like receptors, and transient receptor potential subfamily V1/A1 (TRPV1/A1).[7, 8]

AD pathogenesis encompasses various immune pathways, and many pruritogenic mediators are at play.[3, 8, 9] The pruritogenic mediators consist of proteases, lipid mediators, neuropeptides, opioids, and various cytokines. Various receptors [transient receptor potential ankyrin 1 (TRPA1), TRPV1, protease-activated receptor-2 (PAR2), gastrin-releasing peptide receptor (GRPR), and Mas-related G proteins], secreted molecules (histamine, nerve growth factor (NGF), substance P (SP), and proteases), and cytokines/chemokines (thymic stromal lymphopoietin (TSLP), interleukin (IL)-2, IL-4, IL-13, and IL-31) are implicated as mediators of chronic pruritus.[9] The role of histamine as a pruritogen is highly debated, and histamine effects may be restricted to acute itch.[10] These chemical mediators originate from complex interactions between keratinocytes, inflammatory cells and nerve endings, coupled with upregulated immune cascades, epidermal barrier function, and potential penetration of Type I allergens into the skin.[11] Several factors, including pH gradient, skin barrier integrity, irritant exposure and the microbiome, modulate the impact of these interactions on neurons.[12] Skin damage from dry skin, genetic lesions, or chronic scratching causes the release of epithelial cell-derived cytokines, such as thymic stromal lymphopoietin (TSLP) and IL-33, which can directly activate the pruriceptors.[13] Keratinocyte-derived proteases, such as kallikreins (KLK)s and cathepsin S, can also trigger itching through cleavage-based activation of the PAR2 and MrgprC11. However, whether KLKs activate neuronal PAR2 directly is not yet clear.[13] Immune cells may modulate itch-sensory neurons through the expression of certain cytokines, such as IL-4 from T helper 2 (Th2) cells, mast cells, and basophils, which can exacerbate the itch sensation in atopic dermatitis. Histamine and tryptase from mast cells and basophils can activate G-protein-coupled receptors such as H1/4R, as well as PAR2. While these receptor–ligand interactions have been linked to itching, and immune cells are known to produce these ligand mediators, the precise cellular sources in the context of specific itch disorders is still under investigation.[13]

TSLP is an IL-7 cytokine produced by keratinocytes and mastocytes. It plays a key role in itching through its specific receptor present on neurons, without lymphocyte intervention.[14] Its production is highly increased in AD and initiates an activated T helper 2 (Th2)-type inflammatory response by dendritic cells.[15] The Orai1/nuclear factor of activated T-cells (NFAT) calcium signaling pathway is an essential regulator of TSLP release from keratinocytes, the primary epithelial cells of the skin. TSLP then acts directly on a subset of TRPA1-positive sensory neurons in order to trigger robust itch behaviors.[15]

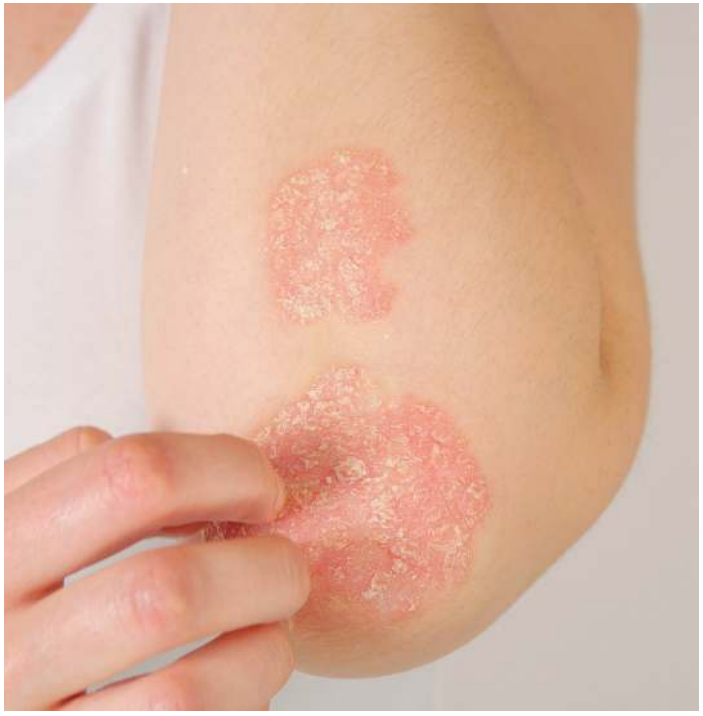
IL-31 is another cytokine that is primarily secreted by activated Th2 cells.[16] IL-31 induces a distinct transcriptional program in sensory neurons and the outgrowth of sensory neurons in a STAT3-dependent manner.[17] The IL-31 translational effect (nerve elongation) may be involved in skin hypersensitivity to pruritogenic trigger factors, especially in patients with AD.[17] **Prolonged itch may be initiated by the overexpression of IL-31 and the promotion of sensory neuronal outgrowth and stimulation.[18]**

Type 2 immune inflammation, the dominant pathway involved in itching, is driven by innate type 2 ILC and Th2 cells as well as their cytokines, such as IL-4 and IL-13.[19] Il-4 and IL-3 directly activate sensory neurons in both mice and humans.[10] Chronic itch is dependent on neuronal IL-4Rα and Janus kinase 1 (JAK1) signaling.[10] Patients with recalcitrant chronic itch that failed other immunosuppressive therapies markedly improved when treated with JAK inhibitors.[10]

Histological investigations have shown that the density of epidermal nerve fibers is higher in the skin of patients with AD.[20, 21] Epidermal hyperinnervation is probably caused by an imbalance between nerve elongation factors, such as nerve growth factor (NGF), and nerve repulsion factors, such as semaphorin 3A (Sema3A), produced by keratinocytes.[22]

Chronic itch has parallels with chronic pain.[23] Chronic itch can be associated with spontaneous itching, hyperknesis (enhanced itch to a normally itchy stimulus), and alloknesis (itch elicited by an innocuous touch stimulus).

Three general mechanisms may contribute to chronic itch: peripheral sensitization which may occur through PAR-2, central sensitization which may occur through TLR3, and dysfunction of inhibitory interneurons.[24]



Barrier function has long been known to be reduced in the skin of patients with AD. **Filaggrin (FLG) has a key structural and functional role in the epidermis and is important for the formation of the corneocyte, as well as the generation of its intracellular metabolites, which contribute to stratum corneum hydration and pH.** A well-functioning epidermis protects humans from exogenous stressors and helps maintain internal fluid and electrolyte homeostasis. Loss-of-function mutations in the FLG gene result in either a reduction (heterozygous) or complete absence (homozygous) of epidermal FLG and its degradation products, which lead to dysfunction of the epidermis and reduced barrier function.[12, 25]

Itch triggers a need to scratch. Scratching temporarily relieves itch sensations through the activation of pain-sensory fibers, which can inhibit itch sensations at the level of the spinal cord.[26] However, chronic itch sensations can drive persistent scratching responses that, in turn, cause mechanical disruption of the skin. Chronic itch sensations and associated scratching behaviors are components of a dynamic pathological process known as the itch–scratch cycle.[13]

Scratching behaviors exacerbate itch sensation through damage to skin epithelial cells. The epithelial stress response releases cytokines, proteases, and antimicrobial peptides (AMP)s that can activate immune cells to promote inflammation. Keratinocytes may also activate itch-sensory neurons directly through soluble mediators such as cytokines and proteases. Release of neuropeptides from neurons can also cause neurogenic inflammation. In contrast, cytokines and proteases produced by immune cells interface with the sensory nervous system in order to mediate itch.[13]

Management of itching and pain in AD is mostly based on topical therapy, although other therapeutic options such as systemic drugs, phototherapy, balneotherapy, and control of environmental triggers are available.[27] Current progress in the knowledge of the itch process, as well as of the numerous mediators and receptors involved, has led to a large variety of possible therapeutic pathways. Currently, inhibitors of IL-31, IL-4/13, neurokinin-1 (NK1) receptors, opioids and cannabinoids, JAK, phosphodiesterase-4-inhibitor (PDE4) or TRP are the main compounds involved in clinical trials. However, many new targets, such as Mas-related G protein-coupled receptors (GPCR)s and unexpected new pathways must also be explored.[27]

Treating chronic pruritus needs to be targeted, multimodal, and performed in a step-wise procedure, requiring an interdisciplinary approach. The updated and consensus-based (S2k) European guideline on chronic pruritus, which provides AD-specific guidelines, was published in 2019.[28]

A position paper on itch and pain management in AD was co-authored by eleven members of the International Society of Atopic Dermatitis (ISAD/Oriented Patient-Education Network in Dermatology (OPENED) task force and published in 2021.[29]

In conclusion, the understanding of the itch process is constantly expanding. A holistic approach to treating AD patients is essential. In any case, it is beneficial to break the itch/scratching cycle.[3, 29]

KEY MESSAGES

- Itch is the main concern for patients with atopic dermatitis (and their relatives/friends)
- Research on itching (especially in atopic dermatitis) provides numerous targets for the alleviation of itch
- Emollients are useful for both skin dryness and itch alleviation

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THE ROLE OF SKIN CARE IN THE MANAGEMENT OF ATOPIC DERMATITIS: IMPACT ON THE SKIN BARRIER

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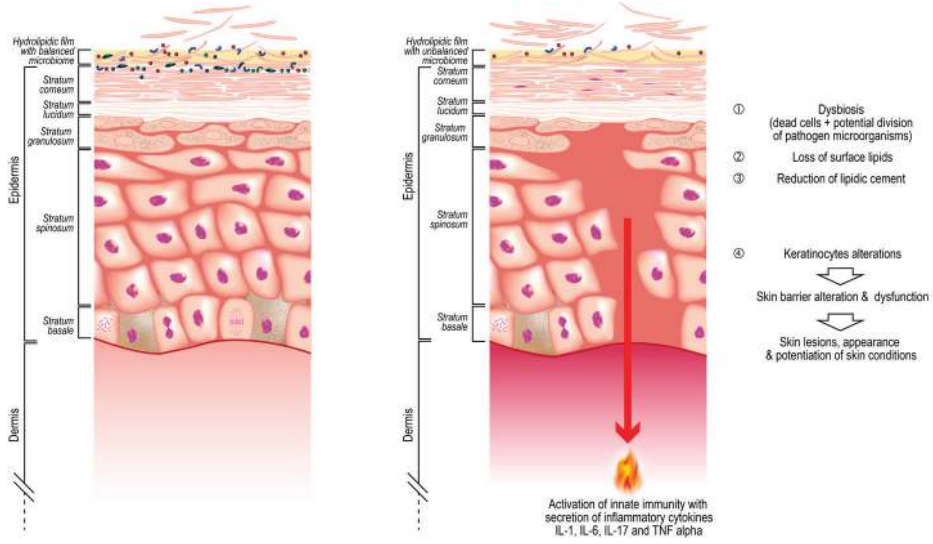
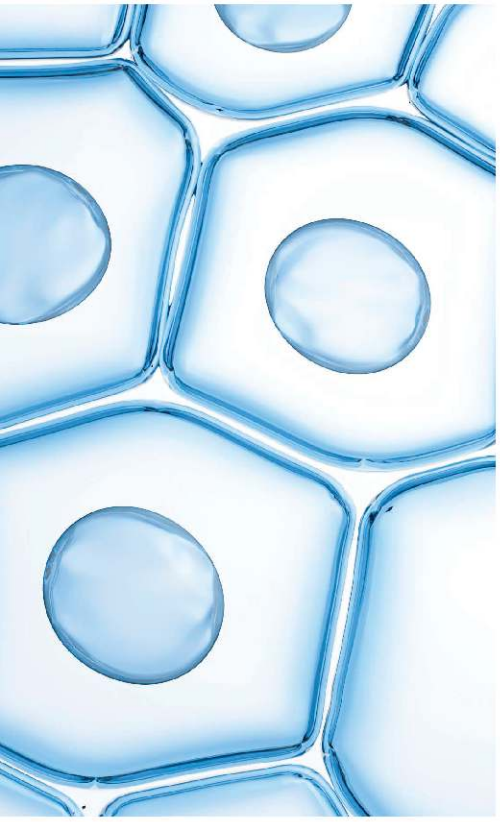
The primary role of the skin is to serve as a barrier, protecting the body from a potential assault from microorganisms, toxic substances and other external physical, chemical or organic factors and to limit transepidermal water loss (TEWL).[1, 2]

In healthy skin, the predominance of hydrophobic substances (lipidic cement) in the intercellular constituents is a significant factor regulating the enzymatic activity and dehydration of the skin. Together with the intracellular constituents, the hydrophilic film is present on the skin as an emulsion and formed from sweat and sebum excretion. It covers the epidermis, thus strengthening the cutaneous barrier and helping the skin to defend the body against TEWL or hyperhydration, particularly during climatic changes.[3] Ceramides are bound to cornified envelope proteins and form the backbone for the subsequent addition of free ceramides, free fatty acids and cholesterol in the Stratum Corneum, while filaggrin is cross-linked to the cornified envelope and aggregates keratin filaments into macrofibrils.[4, 5]





Atopic dermatitis (AD) is the most common chronic inflammatory skin disease.[6] **Genetic predisposition, epidermal barrier disruption, and dysregulation of the immune system are some of the critical components of AD.** Changes in epidermal differentiation and lipid composition lead to a disrupted skin barrier, through a deficiency of barrier proteins, including involucre and tight junction proteins, a modified pH and dysbiosis, a change in the diversity of the skin microbiota with an increase of *Staphylococcus aureus* during flares and an alteration of the immune response leading to the onset or worsening of AD (*Figure 1*).[7]

A such impaired skin barrier enhances allergen penetration into the skin, reduces the natural moisturizing factor (NMF) linked to the filaggrin deficiency, leads to skin inflammation and clinical signs of AD and increases TEWL, related to the deficiency of the hydrolipidic film and inadequate ceramides/cholesterol ratio.[8]

Frequent application of appropriate moisturizers and emollients, such as physiologic lipid mixtures and ceramide-dominant lipid, helps to reduce TEWL, enhances skin hydration, decreases bacterial colonization, and improves skin barrier function, resulting in a decreased need for topical corticosteroid therapy.[8, 9]

International guidelines for the treatment of AD recommend the regular use of moisturizers.[8, 10] Globally, moisturizers include emollients, humectants, and occlusive agents. European guidelines recommend the prescription of moisturizers in adequate amounts, and with a liberal and frequent use in both children and adults.[8] Products with a higher lipid content should always be preferred during winter. In mild-to-moderate AD, a regular use of emollient has been shown to be beneficial as a short- and long-term steroid sparing effect. However, an induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. US guidelines recommend the application of moisturizers as being an integral part of the treatment of patients with AD, with strong evidence that their use reduces disease severity and the need for pharmacologic intervention.[10]

According to these and other guidelines, moisturizers should be applied daily.[8, 10-13] Moreover, an optimal quantity is recommended to improve the course of AD.[14] Fleischer et al. suggests that in children 150 to 200 g/week and in adults 500 g/week of a moisturizer, 125 to 250 g of an ointment in children and 260 to 330 g in adults and 140 to 275 g of a cream in children and 290 to 330 g in adults are optimal quantities to be applied per week. **Despite these clear indications of guidelines and publications, different studies have shown that only one out of three AD patients is compliant with the topical treatment prescribed and one out of two uses less quantity of emollients than actually recommended.**[15, 16]

To date, different types of emollients exist, that contain, among other components, ceramides and cholesterol to restore an effective skin barrier, phytosphingosine which is a natural constituent of ceramides and which stimulates the production of new lipids, as well as essential fatty acids and colloidal oatmeal which has anti-pruritic, anti-inflammatory and antioxidant properties.[17-19]

Particularly in AD, moisturizers require a strong necessity for efficacy, extreme tolerance, the absence of side effects such as burning or tickling sensations, and an excellent sensoriality in order to encourage compliance and thus to be able to provide long-lasting benefit.

As an example, a specific moisturizer (Atoderm® Intensive baume) has been developed by Laboratoires NAOS. This moisturizer contains the Lipigenium™ complex made of phytosphingosine which helps the skin to rebuild its barrier by activating the ceramid neosynthesis and which has been shown to restore the filaggrin expression 37-times over after seven days.[20, 21] Moreover, it contains biomimetic lipids (ceramides 1, 3 & 6, cholesterol, essential fatty acids) that replenish the lipid barrier, enoxolone, which has anti-inflammatory and anti-itching properties through a reduction of the TSLP expression by epidermal cells in atopic environment and palmitoylethanolamide which is anti-itching and improves the skin comfort and quality of life of patients.[22-24] A yet unpublished 6-month study in 130 patients with moderate AD and aged between 6 months and 15 years confirmed that the physician and patient/caregiver SCORAD score had significantly ($p<0.05$) decreased after 6 months, with the patient SCORAD score having significantly changed already after 4 months ($p=0.0086$). Moreover, the patients' quality of life using the IDQoL score had significantly ($p=0.0337$) improved by 89% from baseline at the end

of the study; 76% of the subjects reported no relapse of their AD after 6 months and time to relapse was delayed by more than 20 days in those patients who did relapse.

Another unpublished clinical study testing the anti-itching properties of a gel formulation containing the Lipigenium™ complex showed that the average auto-itching score immediately and significantly ($p<0.0001$) decreased by 18% after the first application and continued to decrease after one (-46%) and 21 days (-70%).

In addition to moisturizing the skin, cleansing of the skin using specifically adapted products (neutral to low pH, hypoallergenic, and fragrance free) plays a key role in the general management of AD. The skin must be cleansed thoroughly but gently and carefully, in order to get rid of crusts and mechanically eliminate bacterial contaminants in the case of bacterial super-infection. Bath oils are a valuable addition for skin care, especially in babies and children.[8, 10]

It is important that the skin be dried gently after bathing and that emollients are applied systematically afterwards, to improve the skin barrier function and to moisturize the skin.[25, 26]

KEY MESSAGES

- Skincare products are useful in the protection and the reinforcement of the skin barrier for patients with atopic dermatitis
- Skincare must include both emollients and cleansing/bathing products
- Topical therapy has to be adapted to the specific needs of each single patient
- Emollients and cleansing products need to be well tolerated and pleasant to use, in order to encourage suitable compliance from the patients

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NOTES

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