Atopic dermatitis: recent insight on pathogenesis and novel therapeutic target

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Summary

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. It affects infancy, but it is also highly prevalent in adults and it is one of the disease burdens for the patients and their families. Nowadays, AD is recognized as a heterogenous disease with different subtypes with variable clinical manifestations which is affected by the impairments of the skin barrier. The severity of AD dictates the level of treatment. Current AD treatment focuses on restoration of the barrier function, mainly through the use of moisturizers and corticosteroids to control the inflammation, topical calcineurin inhibitors, and immunosuppresive drugs in the most severe cases. However, targeted disease-modifying therapies are under investigation. The most recent findings on the skin microbial dysbiosis is a promising future direction for the development of new treatments. We need to improve the understanding of the complex microbiome-host interactions, the role of autoimmunity, the comparative effectiveness of therapies and the ways to appropriately implement the educational strategies. *(Asian Pac J Allergy Immunol 2016;34:98-108)*

Keywords: *atopic dermatitis, skin barrier, skin microbioma, anti-inflammatory therapies, dietary factors, biologics*

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Submitted date: 30/10/2015
Accepted date: 10/2/2016

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. It affects between 15% and 30% of children and 5-10% of adults.[1] Although it most often starts in infancy, it may also have a later onset, between the ages of 18 and 20 years or older.[2] This adult-onset is known as the adult-onset AD, a subset of AD, clinically characterized by a nonflexural rash distribution and atypical morphologic variants, such as nummular or prurigo-like lesions. Quality of life of patients with AD and their families are impaired by interrupted sleep, itching skin conditions, fear of recurrence and in some cases, have psychosomatic comorbidities.[3]

AD is recognized as a multifactorial, heterogenous disease characterized by different clinical phenotypes based on its complex interactions among the susceptibility genes, the host's environment, defects in the skin barrier function and immunological defects that result in the activation of multiple inflammatory pathways.

Specific genetic mutations of the genes involved in the formation of the epidermal skin barrier, such as the mutations in the FLG gene (encoding filaggrin), among null mutation is the strongest known risk factor, and genes encoding proteins of the epidermal differentiation complex [4]. Other loci, mostly implicated in immune dysregulation of the innate and adaptive immune systems have also been identified.[5]

More recently, the genome-wide associations study have led to the discovery of new risk loci correlated with the autoimmune regulation, including candidate genes with roles in the regulation of innate host defenses and T cell function; there appears to be a genetic overlap between other autoimmune and inflammatory disorders.[6]

The progression of the disease from the acute to the chronic stage is a crucial step and much interest has focused on highlighting its mechanisms underlying this immunological shift.

Additionally, advanced information about the role of skin microbioma and its host-microbiome interactions of the pathogenesis of the disease have emerged.[7]

Therefore, a precise understanding of the pathogenetic mechanisms underlying AD is critical for the development of more effective management strategies, also including strategies targeted to modulate the immune system and manipulate the skin microbiome without detracting the importance to restore the skin barrier's function.

The current review summarizes the main AD pathogenetic mechanisms, including more recent findings, gives an overview on current therapeutic strategies and outlines some future lines of research.

Pathogenetic mechanisms

Skin barrier impairment

The composition of the skin barrier is very complex, but one of the major constituents of the barrier is the outermost layer of the epidermis, the stratum corneum. The cornified envelope is composed predominantly of proteins, including filaggrin, loricin, involucrin, and others, and an outer lipid layer that is primarily made up of long-chain ceramides.[8] The stratum corneum provides protection from various environmental stimuli, including allergens, irritants, physical changes, and microbial infection, and also prevents increased trans-epidermal water loss (TEWL).

Epidermal barrier failure is the hallmark of AD and represents the main cause of the subsequent release of pro-inflammatory mediators.[9] Filaggrin gene defects are at the center of this mechanism and are closely associated with AD.[4]

Filaggrin is involved in the development of keratinocytes to maintain the epidermal integrity, and it is an important marker of keratinocytes differentiation. Degradation products of filaggrin contribute to form the natural moisturizing factor (NMF) that plays some role in the maintenance of the skin surface pH and water, thus preserving the barrier function of the stratum corneum.

Inflammation itself is also able to induce functional filaggrin defects through down-regulation of filalgrin production or filaggrin maturation.[10]

The lipids in the epidermis are composed of three major components, ceramides, cholesterol, and fatty acids with the ratio of approximately 3:1:1.

Ceramides, with their long-chain fatty acids, are present in the stratum corneum and are hypothesized to provide moisture-preserving function in the skin.[11] In patients with AD, there is a decrease in ceramide levels, and abnormal ceramide profiles may affect the skin's permeability.

But on the other hand, short chain ceramides are elevated in AD, leading to aberrant lipid organization and defective skin barrier function, and are associated with AD severity independent of FLG mutations.[12]

Tight junctions may also contribute to an important diffusion barrier of the human skin.

Mutations in genes involved in tight junctions [13] also lead to skin barrier disruption.

Immune dysregulation and inflammatory pathways

As components of the innate immunity, antimicrobial peptides (AMPs), generated by keratynocites, play a key role in the clearance of pathogens and in maintaining epidermal barrier effectiveness.

The cationic AMP interact with anionic components of bacteria, fungi and viruses, lead to the destruction of the microbial membrane and cell lysis. Moreover, AMP induces the production of several cytokines and chemokines which contribute to the recruitment of neutrophils, monocytes, mast cells and T cells into the skin.

Two main classes of AMPs in the skin are cathelicidin and the human β- defensins 2 and 3 (DEFB-2 and DEF-B3). Both of these have the ability to kill Staphylococcus aureus (S. aureus) in vitro.

In AD skin, cathelicidin and defensins are both reduced.[14]

For this reason, patients with AD are prone to bacterial infections because of the deficiency of DEF-B2 and DEF-B3 as well as the development of severe viral infections, such as eczema vaccinatum and herpeticum eczema due to the deficiency of cathelicidin.[15]

The recognition of pathogen-associated molecular patterns by pattern-recognition receptors (PRRs) help protect organisms from microbial pathogens.

Mutations in PRRs such as toll-like receptors (TLRs) and nucleotide-binding oligomerization domain like receptors (NLRs) are associated with susceptibility to skin infections by microbial pathogens, such as S. aureus and Malassezia furfur (M. furfur), and play roles in the initiation and exacerbation of AD.

Furthermore, levels of the antimicrobial sphingolipid metabolite sphingosine are also reduced in the skin of AD patients. The sphingosine

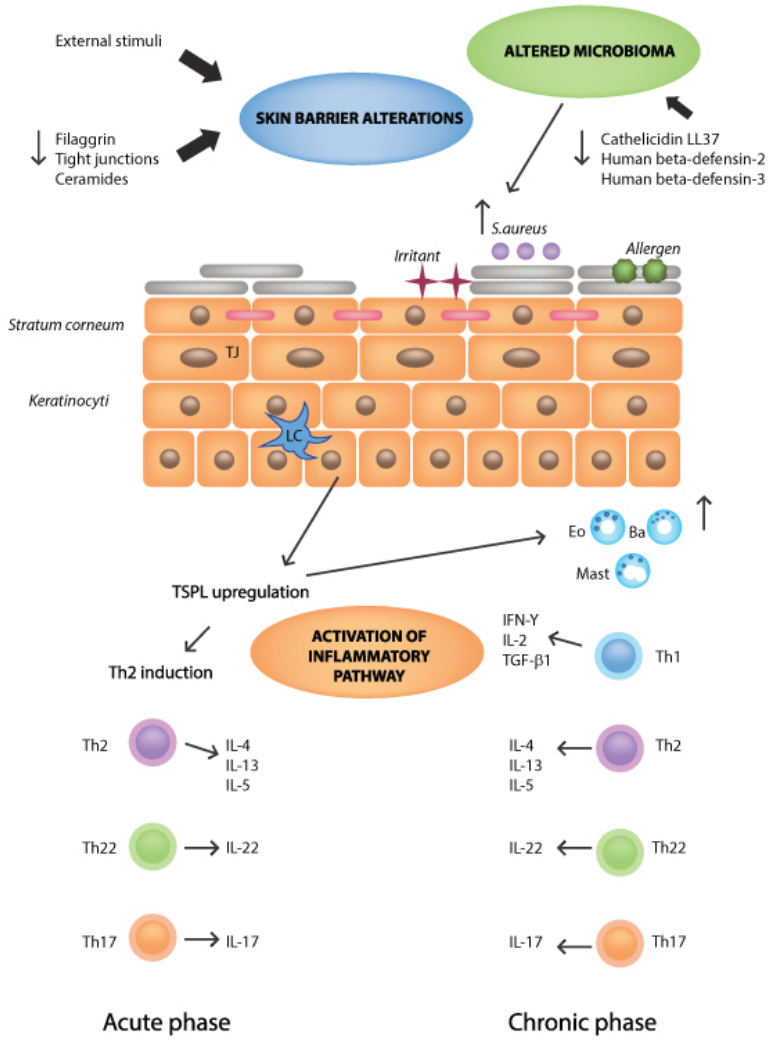

Figure 1. Schematic summary of main pathogenetic alterations of AD. AD is characterized by multifactorial pathogenesis including skin barrier dysfunctions, alterations of microbiota and activation of several inflammatory pathways. Filaggrin and tight junctions genes mutation and reduced ceramides levels contribute to the alterations of skin barrier function. Moreover alterations of microbiota and colonization of S.aureus impair skin barrier. These alterations results in an increased Th2 response mediated through an overexpression of TSLP by keratinocytes. In AD is present an immunological biphasic response with an initial prevalent Th 2 cytokines profile, IL-4, IL-5 and IL-13, with the coexistence of Th17 and Th22 responses. During the chronic phase there is a switch to Th1 cells with Th2, Th17 and Th22 involvement.

deficiency is from decreased levels of ceramides as a substrate and diminishes the activities of its metabolic enzyme acid ceramidase, to further assist the colonization of S. aureus in patients with AD.[16]

Keratynocytes (KC) are not only essential for the innate immune system by detecting the microbial flora via PRRs but also the subsequent production of AMP resulting in the production of cytokines which mediate responses of both the innate and adaptive immune systems.

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine produced in high amount by keratinocytes. TSLP is expressed in the epidermis in the lesions of AD, and has been found to be a crucial factor in activating the Th2 response.[17]

A Th2-biased immune response is closely linked to the acute phase of AD.

Classically, the inflammation in AD is described as a biphasic response with an initial Th2-dominated cytokine profile. Th2 cells are critical for inducing isotype class switching to IgE synthesis and favoring the differentiation of eosinophils.

The Th2 cytokines (i.e., IL-4, IL-5 and IL-13) are significantly increased in the acute phase of AD.

IL-4 and IL-13 are responsible for the differentiation of allergen-specific Th2 cell, which play an important role in the initiation of inflammation. In addition to triggering isotype switching to IgE, Th2 cells also upregulate the expression of adhesion molecules on endothelial cells. IL-13 is known to be a major stimulator of inflammation and tissue remodeling at the site of Th2 inflammation.[18,19]

IL-22 is produced by Th22 lymphocytes and NK cells which have been known to contribute to the acute phase of AD because it down-regulates the skin barrier function,[20] along with IL-31, which also induces pruritus. Both IL-22 and IL-31 serum levels have been positively associated with the severity of AD.[21]

The chronic phase is characterized by a Th1-predominant paradigm. Th1 cells are characterized by the production of IFN-γ, IL-12 and IL-2, TGF-β1 and other cytokines.

IFN-γ acts as a promoter of chronic inflammation, as well as a strong stimulant of tissue remodeling by regulating the plasminogen activator inhibitor type 1 (PAI-1) and tissue-type plasminogen activator (tPA).[22] IL-12, a Th1 cytokine, promotes the development and proliferation of T cells and NK cells, and induces IFN-γ production. IL-12 is elevated in the chronic lesions but not in acute lesions of AD. The high level of IL-12 p40 mRNA expression in chronic AD lesions may be down-regulated by treatment with corticosteroids.[23]

T helper cells 17 (TH-17) represent a recently discovered subpopulation of distinct cell lines compared to TH1 and TH2. They have the ability to secrete IL-17, a proinflammatory cytokine.

They are thought to play a crucial role as mediators of inflammation and autoimmunity.

TH17 are known to characterize the psoriasis, which is classically considered a TH17-driven disease with a TH 22 component, while AD is considered a TH2 centered disease.

Recently, the characteristics of the Asian AD phenotype have been identified and compared to the European American AD phenotype.

Asian AD phenotype is similar to the European AD phenotype (including high serum IgE level) but has a higher TH17 polarization, like psoriasis. The Asian AD phenotype's intermediate cytokine profiles lies in the middle of AD and psoriasis.[24]

The discovery of the Asian AD as a unique immune phenotype provides the rationale to test targeted strategies classically used in psoriatic patients, in addition to TH2 targeted strategies.

In recent years, there is renewed interest about its possible role in the autoreactivity or the pathogenesis of AD.[25]

A subgroup of patients with AD shows IgE reactivity to human antigens.

The spectrum of IgE reactive autoantigens seems to be very broad, including a variety of human protein antigens, several of which have been characterized at the molecular level.

The phenomenon of autoreactivity can be induced during the switch from a predominantly TH2 inflammatory response, typical of the acute phase, to a predominantly TH1 cytokine pattern that can perpetuate the inflammatory response.

It has been hypothesized that as a consequence of the inflammation and scratching, some human and never before recognized epitopes may be released and exhibited; may the recognition of these self-antigens contribute to the autoreactivity response of the immune system.

The results from a recent systematic review showed that the IgE autoreactivity in present in a third of patients with AD, confirming earlier observations that IgE autoreactivity occurs only in a subgroup of patients with AD. The pathogenetic role of autoimmunity in AD remains to be determined.[26]

Role of food allergy and aeroallergens

Many triggers of AD such as food allergens and aeroallergens have been reported.

Serum IgE can be regarded as a clinical biomarker to distinguish "extrinsic" AD (IgE-associated AD) and "intrinsic" AD (non-IgE-associated AD), identifying two different AD phenotypes.

For patients with the so called extrinsic phenotype, the external allergens play a crucial role.

Extrinsic AD is characterized by a high total IgE serum levels, in particular allergen-specific IgE.

In the first 2 years of life, up to two-thirds of infants with moderate to severe disease show sensitisation to food allergens.

However, only a minor proportion of sensitized infants have concomitant IgE-mediated food allergy. The prevalence of food allergy in individuals with atopic dermatitis seems to be around 30% in early and severe cases, which is much lower in mildly affected and older children, and rarely in adults.[27]

Dietary restrictions should only be undertaken with clinically relevant food allergies, documented with the oral provocation test. Food elimination diets based solely on the findings of food allergy test results are not recommended.[28]

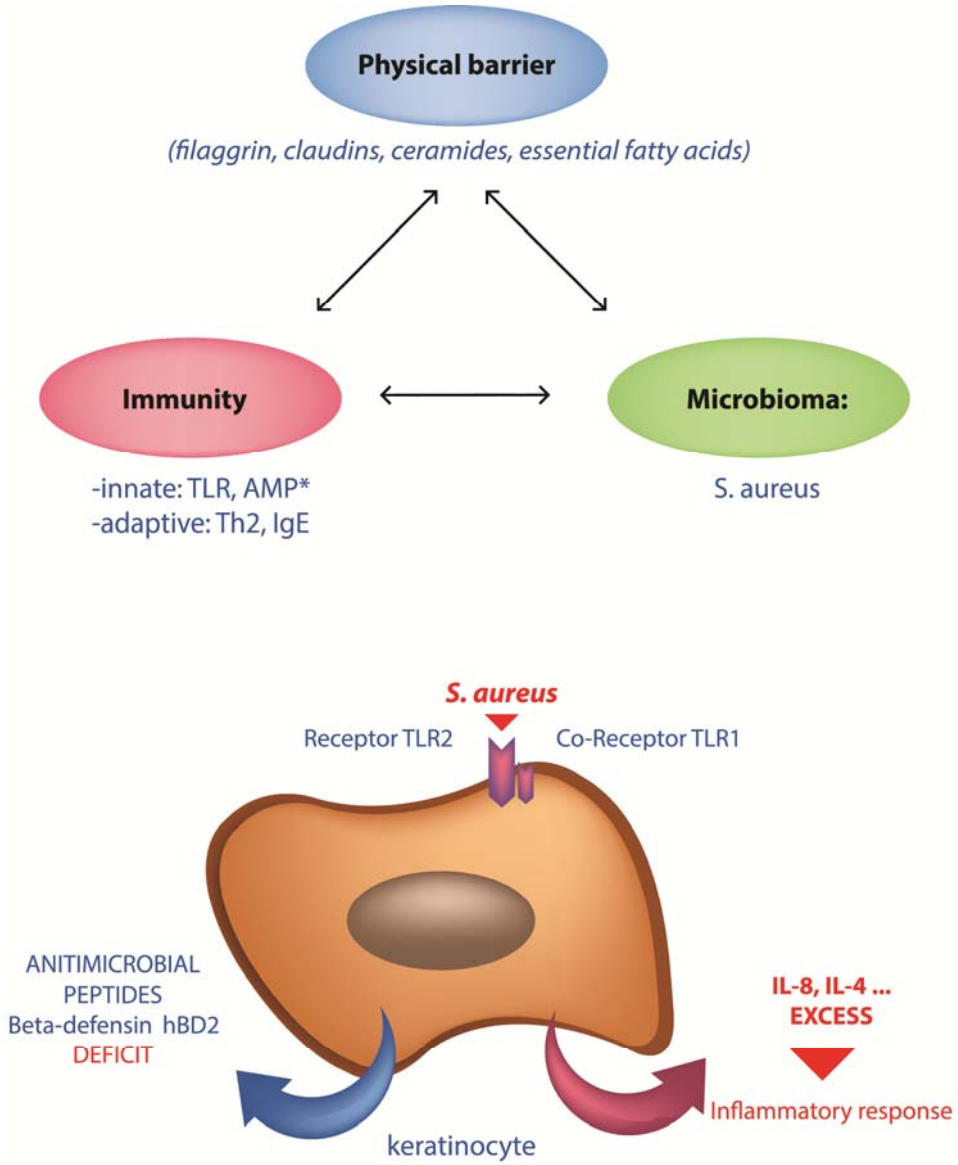

Figure 2. *Main pathogenetic* mechanisms and *Toll Like Receptor2 (TLR2) activation*

Even in those individuals with food allergy, effective treatment for AD remains centered on good skin care and topical therapies.

However, the exact nature of the relationship between AD and food allergy is not clear.

It has become clearer that the IgE mediated reactions can also occur as a consequence of eczema, due to the barrier impairment, and not as a cause.[29]

Therefore, it seems that the association between AD and allergy is complex and that different associations can exist, or co-exist.

As children grow older, the sensitization pattern shifts towards inhalant allergens. Such exposures may contribute to flares. Among the general adult AD patients, more than 85% have aeroallergen specific IgE, mostly against dust mites.[30]

The exact role of aeroallergens in AD pathogenesis is also controversial, because inhalation may induce the release of proinflammatory cytokines in the skin, but avoidance measures have not been consistently demonstrated to be helpful, especially in adults with

severe conditions, whereas some efficacy has been demonstrated in children.[31]

The skin microbiome in atopic dermatitis: a new emerging role

The skin colonization by numerous species of bacteria, fungi and viruses are known as skin microbiome. We have known for many years that the community of bacteria changes on the skin during AD; S. aureus is detectable in more than 90% of AD skin while it is detectable with much lower frequency in healthy skin. Although it is thought to play an important role in the pathogenesis of the disease, it is unlikely that the association is clearly one of cause and effect as elimination of S. aureus does not resolve the disease.

The novel molecular techniques have allowed comprehensive examination of microbial community and have described the magnitude of dysbiosis seen in AD.

Aside from the increased colonization of S.aureus in the skin of AD patients, 16S rRNA DNA sequencing has also revealed an increased colonization of S. epidermidis during flares.[32]

Although the function of increased S. epidermidis colonization is still unclear, this observation suggests that the commensal community may also modulate AD pathogenesis.

Emerging recent findings of the skin microbiome among patients with immunodeficiency suggest that the immune dysregulation may influence the microbioma and in turn, allow the microbiome to interact with the host, contributing to the pathogenesis of the disease.[33]

Overall, the role of the skin microbiome is more complex and interesting than previously thought. It can be used in the future to test the use of probiotics/prebiotics to see whether it can maintain microbioma diversity as one of the preventive measures.

Management

Overall management of AD is aimed to extinguish the symptoms and in the long run, control the disease as well as to empower the patients and their families to obtain the best possible care and quality of life by utilizing educational strategies.

Therapeutic strategies

Successful treatment of AD requires a multipronged approach.

The main goal of therapy for AD is the restoration of the skin barrier, the inhibition of the inflammatory reaction in the skin and relief from the itch.

Basic treatment: moisturizers

Moisturizers are externally applied compounds composed of multiple components, aiming to maintain skin integrity and appearance. Moisturizers are generally classified based on their mechanisms of action: occlusives, humectants and emollient. [34]

Moisturizers have been demonstrated to influence the skin barrier function of normal skin decreasing transepidermal water loss and susceptibility to irritants.

The application of moisturizers decreases the symptoms and signs of AD, as well as have a short- and long-term steroid-sparing effect.

Therefore, moisturizers are the mainstay of treatment for AD and should be applied concomitantly with any other treatment. Comparative studies between moisturizers are needed, as well as further research to define an optimal amount or frequency of their applications.[35]

Antinflammatory therapies: topical corticosteroids and calcineurin inhibitors

Topical corticosteroids represent the mainstay of the anti-inflammatory treatment, showing efficacy in the control of both acute and chronic skin inflammation. Corticosteroids mediate their anti-inflammatory effects through a cytoplasmic glucocorticoid receptor (GCR) in targeted cells.

The receptor complex then translocates into the nucleus of the cell, where it inhibits the expression of inflammatory cytokines (transrepression), induces the expression of anti-inflammatory cytokines (transactivation) and inhibits the production of structural cytokines.[36] Transactivation is mainly responsible for the unwanted side effects of glucocorticoids.

One well-performed treatment per day, compared to two, is sufficient to obtain effect of the treatment; so once the symptoms are controlled, treatment should be tapered by reducing the frequency of the applications or potency of the glucocorticoid. [37]

The use of high-potency steroids increases the risk for systemic side effects, however, high-potency steroids also can restore the skin barrier significantly faster than low-potency steroids, and can shorten the duration of treatment.

Topical calcineurin inhibitors (TCIs), (e.g., tacrolimus and pimecrolimus) inhibit the activation of a number of key effector cells involved in AD, including T cells and mast

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Atopic dermatitis is an inflammatory disease in which different cell types and cytochines are involved
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Skin barrier impairment represents the hallmark of the atopic dermatitis
Dysbiosis and microbiome -host interactions play a role in the pathogenesis of the disease

Table 2. Therapeutic strategies

Therapeutic strategies
The mainstay of the treatment are the moisturizers
Anti-inflammatory treatments represent the second-line therapy. They should always be used with the moisturizers. In mild to moderate cases, topical treatments should be used; in moderate to severe cases systemic immunosuppressive drugs can be added
New emerging therapies, e.g biologics are promising

cells; they are macrolides that exert immunosuppression through inhibition of the calcium dependent dephosphorylation of the transcription factor nuclear factor of activated T cells (NFAT) that is required for the transcription of inflammatory cytokines such as IL-2.

There are situations in which topical calcineurin inhibitors may be advantageous over topical corticosteroids and may be useful as a first-line therapy. Topical calcineurin inhibitors can be used in patients who respond poorly to topical steroids or have steroid phobia, and treat face and neck dermatitis. Ineffective, low-potency topical corticosteroids usually result in steroid-induced skin atrophy.[38]

Both topical tacrolimus ointment (0.03 and 0.1% strengths) and pimecrolimus cream (1% strength) have been shown to be effective short-term (3 to 12 weeks) and long-term (up to 12 months) in adults and children with AD.[39]

No relevant increases in the prevalence of cutaneous viral infections have been demonstrated with the use (continuous or intermittent) of TCIs for up to 5 years.

There have been controversies over the safety of the drugs, as rare cases of malignancy have been described in patients treated with TCIs, although a causal relationship has not been demonstrated.

Nowadays, surveillance-studies have reported no evidence of increased malignancy rates in the general pediatric population.[40]

Although a follow-up study over 6 years has shown no increased risk of lymphoma after the use of TCIs,[41] yet there is a need for careful surveillance when such agents are used long-term.

Novel uses of topical anti-inflammatory treatments

A novel tactic has been described, which does not wait for the skin to clinically demonstrate manifestations of AD. This "proactive" approach assumes, based on the histopathological evidence, that the epidermal barrier dysfunction and inflammation are ever-present in AD, even if subclinical.

Thus, after active areas have resolved, in this novel strategy, patients apply topical anti-inflammatory agents intermittently during remission periods to areas previously affected, along with emollients to unaffected skin. This novel approach has been suggested for those subjects who suffer from frequent outbreaks at the same body areas.[42]

Proactive treatment (e.g., once to twice weekly application of mid-potency topical corticosteroids during remission periods) has been shown to be efficacious and well tolerated in clinical trials.

Likewise, proactive application of TCIs two to three times a week to recurrent sites of AD has also been shown to be effective in reducing flare-ups.[43]

Long-term management of mild-to-moderate AD in infants with pimecrolimus cream 1% (PIM) was safe without any effect on the immune system. PIM was steroid-sparing. The data suggest PIM had similar efficacy to TCS and support the use of PIM as a first-line treatment of mild-to moderate AD in infants.[44]

Antibacterials and antiseptics

Patients with AD are predisposed to develop various skin infections due to the skin barrier impairment. Although viral or fungal infection can trigger AD, S. aureus is a frequent culprit as it has been isolated from more than 90% of adult AD patients.[45] However, the clinical relevance of bacterial overgrowth is patient-dependent and there is a lack of good evidence to support the use of antimicrobial and antiseptic preparations to treat AD.[46] Therefore, the continuous use of antibiotics,

regardless of whether they are topical or systemic, to treat non-infected AD, is not recommended.

A short-term treatment with topical or systemic antibiotics (Cephalosporins, penicillinase-resistant penicillins, or clindamycin are preferred) may be beneficial in addition to standard, appropriate treatment if the skin is clinically superinfected with oozing, crusts, pustules and/or fissures.

Bleach baths and intranasal mupirocin may be recommended to reduce disease severity in patients with moderate to severe AD and clinical signs of secondary bacterial infection.[37]

Alternative anti-inflammatory therapies: phototherapy, cyclosporine and antimetabolites

A recent systematic review of RCT conducted in phototherapy adults concludes that phototerapy can be a valid therapeutic approach for patients with AD.

On the basis of the included evidence, ultraviolet A1 (UVA 1) and narrow-band UVB (NB-UVB) seem to be the most effective treatment modalities, among the different forms of phototherapy.

The photoimmunologic effects target key cells in atopic inflammation, such as LCs and keratinocytes, interfering with the cytokine production and decreasing the expression of activation markers such as HLA-DR and IL-2 receptor on CLA+ T cells.

There is still no standard protocol for the optimal dose, duration, and frequency of NB-UVB treatment as well as the optimal treatment dose for UVA1 has not yet been determined. These aspects need to be further evaluated in clinical trials. In addition, the long-term effects of phototherapy should also be investigated.

Cyclosporin A is a potent systemic calcineurin inhibitor that is licensed in many countries as systemic treatment for severe AD in adults. It efficacy has been demonstrated for the treatment of severe, refractory AD in both children and adults, although toxicity, primarily renal, limits its long-term use. Antimetabolites, including mycophenolate mofetil, a purine biosynthesis inhibitor, methotrexate, and azathiaprine, have also been utilized for severe, recalcitrant AD, although the potential for systemic toxicities restrict their use and require close monitoring.[47]

Dietary factors: Probiotics and fatty acids

A recent meta-analysis suggests that probiotics may be useful for the treatment of AD, especially for moderate to severe AD in children and adults, but does not support the benefit of probiotics in infants.[48]

Probiotics/prebiotics may be an option for adjuvant therapy for AD; however, additional research is required in this area before any clinical recommendations can be made.

With respect to fatty acids, a recent Cochrane Systematic Database review concluded that oral borage oil and evening primrose oil, which both contain γ-linolenic acid, does not have any effect on eczema.[49] The review does not provide any information on the long-term use of these products. The long-term use of these fatty acids, as well as the analyses of the key genes variants, may be important and should be considered.[50]

Biologics and other novel therapeutic strategies

Ongoing therapeutic studies in AD focus generally on three aspects: reducing inflammation non-specifically, targeting the T-helper mediated immune response and blocking pruritus.

Omalizumab is a monoclonal antibody that recognizes and masks an epitope in the CH3 region of IgE responsible for binding to the high-affinity FceR on mast cells and basophils.[51] This should ideally prevent the enhanced pathogenic Th2 T cells responses caused by the IgE allergen-specific bound targeted cells.

However, this strategy has not provided any convincing successful therapeutic data for the treatment of AD.

Other monoclonal antibodies, targeted against different cytokines are under investigation.

Several studies with recombinant human IFN-γ demonstrated clinical efficacy correlated with a decreased eosinophilia level in the blood, even with long-term therapy, although this approach has been limited because of its toxicity.

Other strategies include cytokine modulation (e.g., soluble IL-4 receptor; TNF inhibitors), blockade of inflammatory cell recruitment (chemokine receptor antagonists, CLA inhibitors), elimination of B cells (anti-CD 20 monoclonal antibody), inhibition of T cell activation (alefacept, efalizumab), and use of synthetic antimicrobial peptides.[19]

Moreover, different novel treatments targeting pruritus are currently being studied such as the inhibition of chymase-activity, topical antihistamine and antidepressant, m-Opioid receptor (MOR)-antagonist, prostanoid DP1 receptor agonist, cannabinoid receptor agonist and tachykinin receptor antagonist.

Allergen-specific immunotherapies (ASIT) are also being tested for AD management. A recent meta-analysis provides a moderate level of evidence for the efficacy of ASIT in AD management, although these results are based on a small number of RCT.[52] Currently, the best therapeutic response to AD treatment using ASIT is for house dust mite allergen.[53]

Educational strategies

Providing education to the patients and caregivers is an important strategy for the intervention of AD.

The basis of educational programs is to promote individuals with a chronic disease to be able to deal with their everyday life.

Different multidisciplinary educational programs have been established in some countries and their efficacy in terms of decreasing the disease severity and ability to improve the subjective assessment of its severity to work in groups have been demonstrated.[54,55]

Nevertheless, these programs require hard efforts, in terms of personnel and financial resources. For these reasons, other educational strategies have also been employed, including workshops and nurse-led educational session or parental education via standardized video.

The criteria for the selection of a suitable program need to be considered in the context of diverse cultural and financial aspects.[56]

Finally, the educational information and support groups provided by organizations such as the National Eczema Association (http://nationaleczema.org/) can also be useful as they facilitate communication and networking between affected patients and families.

Conclusions and future challenges

For the past 10–15 years, research has shown that the impairment of the barrier function in the skin and cutaneous inflammation play a key role in the pathogenesis of AD.

Thus, the current treatment for AD is directed to inhibit the inflammatory reaction and re-establish the skin barrier function.

Insights into the role that certain cells and cytokines contribute to AD create opportunities for the development of targeted therapy. However, given the complexity of the biological processes involved, none of the tested compounds to date has proven to be the magic remedy.

Another challenge will be to come up with treatment programs that include safer drugs, educational programs, life style interventions and the development of programs that can prevent AD in newborns.

Future research on prevention should examine different types of hydrolyzed formulas, prebiotics and probiotics, as well as enhancement of the skin barrier in infants at different risk levels for developing allergic disease.

Thus, it will be important to better characterize the immune pathways leading to the different phenotypes of AD, as therapies may vary in their effectiveness for treatment of different forms of AD.

An understanding of the genes responsible for individual variation in response to therapy will be tied to the development of pharmacogenetics and the targeting of effective therapies to the different phenotypes of AD.

Key points
Atopic dermatitis is an inflammatory disease in which different cell types and cytokines are involved
Both innate and adaptive immunity defects play a role
Skin barrier impairment represents the hallmark of atopic dermatitis
Dysbiosis and microbiome -host interactions play a role in the pathogenesis of the disease
The mainstay of the treatment are the moisturizers
Anti-inflammatory treatments represent the second-line therapy. They should always be used with the moisturizers. In mild to moderate cases, topical treatments should be used; in moderate to severe cases systemic immunosuppressive drugs can be added
New emerging therapies, e.g biologics are promising

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