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Approaching atopic dermatitis treatment differently: from skin barrier preservation to allergen-specific immunotherapy

"A normal and efficient skin barrier is essential in order to prevent or reduce the penetration of allergens, micro-organisms and irritants. For this reason, a restoration of altered skin barrier should be considered as a primary therapeutic goal in atopic dermatitis."

KEYWORDS: antimicrobial peptides ■ atopic dermatitis ■ skin barrier dysfunction ■ specific immunotherapy

Atopic dermatitis (AD) is a common inflammatory, itching skin disease [1]. Epidemiological studies show that one in every four children suffers from AD. In addition, 3% of the adult population are affected worldwide [2]. The clinical picture of AD is dominated by chronic eczematous skin lesions in typical localizations [3]. Itchy skin and rashes are the most common symptoms of AD. Skin lesions are often observed on the face, inside the elbows and behind the knees, and on the hands and feet [4]. Furthermore, clinically unaffected skin in AD is abnormal. In fact, skin is frequently dry and shows a greater response to irritants than normal healthy skin [5]. Microscopic studies reveal a perivascular T-cell infiltrate in unaffected AD skin that is not seen in normal healthy skin [6]. There is a marked infiltration of activated CD41 memory T cells in acute AD [7]. APCs in lesional and nonlesional skin bear IgE molecules [8]. Mast cell degranulation can be observed. Eosinophil cells can also contribute to the inflammatory condition. In the chronic phases of the disease T cells remain present, although in smaller numbers than seen in acute AD [9]. Chronic AD skin lesions undergo tissue remodelling caused by chronic inflammation. Although AD may occur at any age, it most often begins in infancy and childhood. The etiology of AD remains unknown so far, but the disease seems to be a result of a combination of genetic and environmental factors [10]. Children are more likely to develop this disorder if their mother or father, or both, have had AD or have had other allergic conditions such as allergic rhinitis or asthma [11]. While some people outgrow skin symptoms, approximately three-quarters of children with AD go on to develop hay fever or asthma in the following years [12].

AD & skin barrier dysfunction

Under normal conditions, skin provides an effective barrier between the organism and the environment, preventing the invasion of pathogens and blocking chemical and physical assaults, as well as controlling and tuning water and solute loss [13]. Skin barrier alterations in AD have been extensively described by Elias and Schmuth [14]. Alteration in skin barrier function plays a major role in the pathogenesis of AD [15]. A deficit in lipid components (i.e., ceramide) has been described in AD. A deficit in filaggrin synthesis has been demonstrated in up to 30% of AD patients [16]. Filaggrin is crucial for efficient hydration of the skin [17]. The antimicrobial barrier is also compromised in AD. This alteration could favor colonization of lesional and nonlesional skin by *Staphylococcus aureus*. In fact, in AD, in contrast to psoriasis, a reduced synthesis of antimicrobial peptides has been observed [18]. This alteration of a component of innate immunity could be one of the mechanisms responsible for the increased incidence of bacterial skin infections observed in AD patients. AD is characterized by dry skin, even skin that is nonlesional. In addition, AD is characterized by an increase in transepidermal water loss [19]. In healthy skin, the ceramide complex, an important component of the skin barrier, serves as the major water-retaining molecule in the extracellular space of the cornified stratum, contributing to a normal hydration of the skin. The barrier function of these complex structures is provided by a matrix of structural proteins, which are bound to ceramides [20]. A normal and efficient skin barrier is essential in order to prevent or reduce the penetration of allergens, micro-organisms and irritants. For this reason, a restoration of altered skin barrier



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should be considered as a primary therapeutic goal in AD [21].

AD as an allergic disease

It has been found that people with AD have a low level of IFN- γ , a cytokine that is essential to the healthy function of the body's immune system, and a high level of other cytokines such as IL-4, IL-5 and IL-13, which lead to allergic reactions. The immune system can become dysregulated, favoring inflammation processes in the skin, even in the absence of a major infection [22]. AD is frequently associated with allergic respiratory disease and is often the first manifestation of allergic disease [23]. Atopy is associated with the manifestation and severity of AD, especially in children. Sensitization to aeroallergens (mites and pollen) has been shown to increase the risk of developing AD and also AD severity [24]. Aeroallergens could also be a trigger for exacerbations in AD. Up to 80% of patients suffering from AD are sensitized against different aeroallergens and food allergens. In fact, sensitization to inhalant allergens is often seen in patients with AD [25].

Traditional therapeutic approach to AD

The most common feature of AD is severe dryness of the skin resulting from a dysfunction of the skin barrier, causing an increase in transepidermal water loss. This alteration typically causes intense itching and inflammation. Basic therapy of AD should comprise optimal skin care, addressing the skin barrier defect with the regular use of moisturizing and emollient topical products and skin hydration [26]. The regular use of emollients is important for addressing this problem, and, together with skin hydration, it represents the cornerstone of the general management of AD [27]. Topical corticosteroids in both cream and ointment formulations have been used for many years to treat AD and other autoimmune diseases affecting the skin [28]. New medications known as immunomodulators have been developed aiming to control inflammation and reduce immune system reactions when applied to the skin. Tacrolimus ointment and pimecrolimus cream are examples of this class of medications [29]. They not only reduce flares but also maintain skin texture and reduce the need for long-term use of corticosteroids. However, corticosteroids and immunomodulators are not etiologic treatments of AD. These approaches control symptoms and suppress inflammatory reactions but they do not treat the causes of this skin condition.

Skin barrier function restoration

Alteration of the skin barrier is probably the main physiopathological aspect of AD [30]. For this reason, restoration of efficient skin barrier function should be a therapeutic goal in the management of AD patients. Moisturizers should be recommended to the majority of AD patients, and should be part of their daily skin care. This is because moisturizers have the potential to reduce the quantity of topical steroids necessary to control the disease [31]. Moisturizers result in an increase of skin hydration and restoration of the skin barrier function and play a prominent role in the long-term management of AD [32]. The benefit of emollients may be explained by the inhibition of the loss of water content of the skin and the restoration of the fatty component of the outer layer of the skin. However, the effects of the majority of emollients are limited to an increase in the water content of the epidermis and they are not able to correct the multiple skin barrier alterations observed in AD (e.g., deficit in lipid content, deficit in filaggrin and deficit in antimicrobial peptides of the skin). Recently, increased interest has been directed to isoleucine. Isoleucine is an essential amino acid that is a highly specific β 2-defensin inducer in epithelial cells [33]. Therefore, there is a strong rationale for the use of this compound in AD subjects. Recently, a topical product containing isoleucine and an inhibitor of bacterial adhesion to epithelial cells (rahnose derivative) has been developed as a coadjuvant treatment for AD [34]. This particular topical product in cream formulation also contains ceramide. Therefore, this product could be considered an efficient topical emollient treatment addressing the complex aspects of skin barrier defects observed in AD.

Specific allergen immunotherapy as an option

In the scientific literature, some anecdotal and case reports can be found suggesting clinical benefit from allergen-specific desensitization (specific immunotherapy [SIT]) in AD [35]. SIT is clinically efficacious in the therapeutic management of allergic asthma, allergic rhinitis/conjunctivitis and stinging insect hypersensitivity [36]. There is some evidence suggesting that SIT could also be effective in the treatment of AD in patients with aeroallergen sensitivity. At least 12 placebo-controlled trials have been conducted to evaluate the efficacy of SIT in AD patients [37]. Nine trials (75%) reported significant positive effect of SIT in comparison with placebo. A recent randomized, double-blind, dose-response, multicenter

trial with house dust mite SIT in 89 subjects aged 18 years or above with chronic AD with proven sensitization to dust mite showed that the Scoring Atopic Dermatitis (SCORAD) score, the primary end point of the trial, decreased in the three dose groups in a dose-dependent manner and was significantly lower in the two high-dose groups compared with the low-dose group after 1 year of SIT [38].

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In comparison with subcutaneous SIT, sublingual immunotherapy (SLIT) is considered a more convenient and safer approach for the treatment of some forms of allergies. So far, there are no conclusive data regarding the efficacy and safety of specific SLIT in patients with AD. In a randomized, double-blind trial, a total of 56 children with AD were treated with SLIT house dust mite (HDM) allergen extracts or the corresponding placebo for 18 months [MILANI M, DATA ON FILE]. Significant improvement of SCORAD scores in the treated group was observed after as few as 9 months of treatment. A multicenter trial evaluating the efficacy of SLIT in 96 AD patients with HDM sensitivity showed that this therapeutic option is efficacious and safe [39]. Patients were treated with SLIT for at least 12 months. SCORAD was evaluated at baseline and after 12 months of treatment. At baseline the SCORAD value (mean $\pm$ standard deviation) was 43.3 ± 13.7 (range: 18–84). After 1 year of SLIT, the SCORAD value was reduced to 23.7 ± 13.3 (range: 0–65; $p = 0.0001$; unpaired t-test vs baseline). This was a 46% reduction in SCORAD value in comparison with baseline. A significant improvement, defined as a SCORAD reduction of $>30\%$, was observed in 57 out of 96 patients (59.2%). Treatment with SLIT also allowed a gradual reduction of concomitant corticosteroid and immunosuppressant therapies. More recently, these data have been confirmed by an 18-month randomized trial in which 65 pediatric patients with mild-to-moderate AD and HDM sensitization were treated with SLIT with natural HDM extracts or with standard treatment [MILANI M, DATA ON FILE]. After 18 months the SCORAD value had significantly decreased in the SLIT-treated group (-35% vs baseline) but remained stable in the control groups. Taken together, these data suggest that

SLIT can modulate the immune system in patients with AD and HDM sensitivity.

Conclusion & future perspective

AD is a common inflammatory, itching skin disease affecting a large number of children and adults. While some people outgrow skin symptoms, approximately three-quarters of children with AD go on to develop hay fever or asthma. AD is frequently associated with allergic respiratory disease and is often the first manifestation of such diseases. Patients suffering from AD are at high risk of developing allergic rhinitis and asthma. Skin barrier function defects demonstrated in AD, such as reduced synthesis of filaggrin and reduced levels of antimicrobial peptides such as $\beta 2$ -defensin and cathelicidine, could play a crucial role in the initiation processes involved in the pathogenesis of this disease. The inflammatory process in the skin of patients with AD starts with allergen uptake by epidermal dendritic cells. This process is facilitated by the defect in skin barrier function observed in AD. So far, no treatments are available addressing the causes of AD. Basic therapy of AD comprises optimal skin care, emollient creams, topical corticosteroids and/or topical calcineurin inhibitors. Despite a strong rationale, hyposensitization with SIT is not an established strategic treatment of AD. However, different controlled trials have shown that subcutaneous immunotherapy and SLIT with HDM allergen extracts in both adults and children with AD with positive skin test toward HDM allergens are effective in reducing the SCORAD index and reducing, in the meantime, the need for topical corticosteroids. The knowledge regarding the pathological mechanisms involved in AD underlines the relevance of the skin barrier defect with its deficit of filaggrin, reduced levels of ceramides and reduced synthesis of antimicrobial peptides. These alterations of the skin barrier could facilitate the penetration of allergens through the skin. Specific topical treatments aimed at restoring an efficient skin barrier function and increasing the synthesis of antimicrobial peptides (such as topical isoleucine) could widen the range of therapeutic tools available for an ‘holistic’ approach to this skin disease.

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