*Update review*

# Atopic dermatitis: Therapeutic concepts evolving from new pathophysiologic insights

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**Recent insights into the relevance of the epidermal barrier function and its interaction with components of the innate and adaptive immune responses in patients with atopic dermatitis (AD) give rise to a number of novel potential treatment options. In particular, the identification of loss-of-function mutations in the barrier protein filaggrin and of a diminished expression of certain antimicrobial peptides in AD skin stimulates new concepts to think beyond the $T_H1/T_H2$ paradigm. This review will focus on these most recent discoveries and will discuss new and corresponding proof-of-concept trials in patients with AD. It will further speculate on novel ways to restore the homeostasis among the 3 major components in AD skin suspected to be clinically relevant. (J Allergy Clin Immunol 2008;122:1074-81.)**

***Key words:*** *Atopic dermatitis, skin barrier function, innate immune system, adaptive immune system, filaggrin, $T_H2$ cells, $T_H17$ cells, immunotherapy, proof-of-concept trial*

The predominant role of cell-mediated immunity in the evolution and persistence of atopic skin lesions is fully appreciated. Nevertheless, it now appears that immunologic abnormalities in patients with atopic dermatitis (AD) exist not only in the adaptive but also in the innate system, as evidenced by the impaired expression of antimicrobial peptides. One of the most exciting discoveries in AD research was the recent identification of genetic aberrations in critical constituents of the epidermal barrier. Some investigators believe that this defect is the primary event in disease pathogenesis, allowing the entrance of large immunogenic protein antigens in the epidermis/skin. We should also not forget that patients with AD exhibit other symptoms, such as an abnormal vascular and sweat response, that cannot be easily explained by either epidermal barrier dysfunction or altered immunity. This is also true for our understanding of the sometimes intractable pruritic sensations so typical of this disease.

*Abbreviations used*
AD: Atopic dermatitis
DC: Dendritic cell
FLG: Filaggrin
LEKTI: Lymphoepithelial Kazal type inhibitor
MMF: Mycophenolate mofetil
TLR: Toll-like receptor
TSLP: Thymic stromal lymphopoietin
VEGF: Vascular endothelial growth factor

## ROLE OF EPIDERMAL BARRIER DYSFUNCTION IN AD PATHOGENESIS

Dryness of the skin is a hallmark of patients with AD. It is due to a defect in the epidermal barrier and, as a consequence, an increased transepidermal water loss. The barrier itself is the brick and mortar–like structure of the outer epidermal layer.[1,2] Its appropriate function is secured by an interplay of proteins of the keratin cytoskeleton (eg, filaggrin [FLG], involucrin, and loricrin), of intercellular lipids (eg, ceramides) provided by keratinocyte-derived lamellar bodies, and of a set of epidermal proteases, such as the stratum corneum chymotryptic enzyme. The identification of several loss-of-function mutations of the *FLG* gene in up to 50% of all patients with AD[3-6] has evoked a great deal of interest. FLG is a key protein of epidermal differentiation serving as a template for the assembly of the cornified envelope. Its breakdown products critically contribute to the water-binding capacity of the stratum corneum. The fact that at least 50% of all patients do not show any *FLG* mutations and that even those who have mutations grow out of their disease, although this process takes longer than in *FLG*-normal patients,[7] indicates that (1) defects in barrier proteins other than FLG could contribute to barrier dysfunction in AD and (2) compensatory mechanisms must be operative to restore a normal skin barrier function. Mice deficient in either involucrin, envoplakin, or periplakin do not show a major disturbance of skin barrier function, but a triple deletion results in marked deficiency of epidermal barrier function.[8] In addition, mice lacking serine protease inhibitor Kazal type 5 (*SPINK5*), the gene deficient in Netherton syndrome and encoding the serine protease inhibitor lymphoepithelial Kazal type inhibitor (LEKTI), exhibit substantial barrier dysfunctions through uncontrolled epidermal serine protease activity.[9] Concordant with this is the observation that epidermal overexpression of mouse kallikrein 7, a serine protease under the control of LEKTI, mediates skin barrier function.[10] Finally, mice with transgenic expression of human apolipoprotein C1 in the liver and skin display a disturbed skin barrier function and have AD-like symptoms.[11] These examples show that each of the 3 components contributing to

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Disclosure of potential conflict of interest: G. Stingl has provided expert witness testimony for Novartis. T. Jung has declared that he has no conflict of interest.
Received for publication September 5, 2008; revised September 27, 2008; accepted for publication September 29, 2008.
Available online November 7, 2008.

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0091-6749/$34.00

doi:10.1016/j.jaci.2008.09.042

intact skin barrier function (ie, structural proteins, lipids, and proteases) can give rise to abnormal function and therefore offer novel therapeutic options. In general, the stratum corneum and upper epidermis should be amenable for new topical treatments, thus avoiding toxicities potentially associated with systemic therapies. In an effort to substitute lipids, the topical application of a synthetic ceramide showed inhibition of skin inflammation in a NC/Nga mouse model of AD,[12] and a potential topical synthetic pseudoceramide lacked keratinocyte toxicity *in vitro*.[13] These data are concordant with a previous observation that a ceramide-dominant, physiologic lipid–based emollient was well tolerated and improved disease severity in 24 children with AD as an add-on therapy.[14] In addition, a cream containing a preparation of *Streptococcus thermophilus* was claimed to be effective in enhancing stratum corneum ceramide levels in healthy volunteers because of the high levels of neutral sphingomyelinase activity in this organism.[15] On the other hand, topical inhibitors of proteases or protease inhibitors could be effective in restoring the epidermal barrier. Netherton syndrome should be a prototypical disease to test the effect of protease inhibitors because epidermal proteases are overexpressed due to the lack of the protease inhibitor LEKTI. In an attempt to test a protease inhibitor in patients with Netherton syndrome, $\alpha_1$-antitrypsin was administered topically to 5 patients for 3 weeks, and its effect was compared with that of placebo.[16] No difference with placebo was observed, and it remained open whether this was due to a formulation issue or an inferior activity of the drug against stratum corneum trypsin. Although this particular study result is inconclusive, there is good evidence that topical agents interfering with proteases or protease inhibitors could be successful in restoring the skin barrier function in patients with AD.

There exists now a vivid debate as to whether the genetically determined defect of the epidermal barrier is the primary event in AD pathogenesis. Advocates of this concept argue that this defect is an important prerequisite for the entry of large protein allergens of the environment into the epidermis, their uptake by dendritic antigen-presenting cells, and, ultimately, the elicitation of a productive T-cell response. It should be emphasized that some of these exoallergens are not as innocuous as previously thought. Certain pollens, for instance, can promote the production of proinflammatory cytokines, can skew the immune response in a $T_H2$ direction, or both.[17] Researchers claiming that a genetically determined immunodysregulation is the *primum movens* in AD base their theory on the capacity of certain proinflammatory cytokines to modulate the expression of genes of the epidermal barrier, such as *FLG*.[18] Reports that topical calcineurin inhibitors can, at least partially, correct the barrier defect in AD (M. Cork and E. Proksch, unpublished observations) and that gentamicin can restore the production of functional *FLG* chains (I. McLean, unpublished data, 2008) deserve particular attention.

## THE ROLE OF INNATE IMMUNITY IN AD PATHOGENESIS

Clinicians are well aware of the fact that patients with AD have a greatly increased risk of certain types of bacterial *(Staphylococcus aureus)*, viral (herpes simplex virus and pox viruses), and fungal *(Malassezia sympodialis)* infections. One possible reason for this enhanced susceptibility to microbial colonization has been recently identified. Epithelial cells are equipped with a variety of pattern-recognition receptors (eg, Toll-like receptors [TLRs]) sensing different microbial structures.[19] Thus activated, epithelial cells start to produce antimicrobial peptides, including defensins, cathelicidins, dermcidin, and psoriasin. Ample evidence now exists that atopic skin exhibits decreased levels of such peptides and that a $T_H2$-dominated milieu, an IL-10–dominated milieu, or both is responsible for this impairment.[20-24] Plasmacytoid dendritic cells (DCs) are an important component of the innate response. Well endowed with pattern-recognition receptors, including TLR7 and TLR9, they start to elaborate large amounts of IFN-α on activation[25] and can even acquire TNF-related, apoptosis-inducing, ligand (TRAIL)–dependent cytotoxic properties.[26] The skin of patients with AD harbors relatively small numbers of plasmacytoid DCs when compared with the skin of patients with other inflammatory skin diseases, such as psoriasis, contact dermatitis, or lupus erythematosus.[27] This partial deficiency might also contribute to the impaired host defense of atopic skin against a microbial assault.

It has become increasingly evident that components of the innate immune system are linked not only with the adaptive immune system but also with the epidermal barrier function.[28] As a result, therapeutic concepts to improve the antimicrobial defense mechanisms in AD skin might ultimately be beneficial for the epidermal barrier. Because antimicrobial peptides are under the control of epidermal proteases, inhibitors of proteases should ultimately lead to a longer half-life of these antimicrobial peptides, thus potentially improving both the barrier function and the innate immune system. On the other hand, stimulating the production of antimicrobial peptides could be beneficial, as indicated by 2 very recently introduced concepts.

TLR-activated human macrophages showed increased expression of the vitamin D receptor and killed intracellular *Mycobacterium tuberculosis*,[29] a mechanism that was dependent on vitamin D3 and its subsequent production of cathelicidin.[30] Consequently, oral vitamin D supplementation for 3 weeks significantly increased the expression of cathelicidin in lesional, but not nonlesional, atopic or healthy skin in 14 patients with AD and 14 healthy subjects, respectively.[31] A case report series of 11 patients with prurigo, of which 4 had AD, reported a significant clinical response in 9 cases to topical vitamin D3 ointment within 4 weeks.[32] The number of epidermal $Fc\epsilon R1^+$ DCs was increased at baseline and normalized after therapy. Thus vitamin D3 supplementation might be an effective novel therapy to improve innate immunity in AD, a preliminary conclusion that certainly deserves more attention and in-depth investigation.

Buchau et al[33] reported on a second approach to increase keratinocyte-derived antimicrobial peptides. The calcineurin inhibitor pimecrolimus enhanced the expression of cathelicidin, CD14, and β-defensin 2 and 3 in response to TLR2/6 ligands *in vitro* and consequently inhibited the growth of *S aureus*. Whether this is also true *in vivo* in patients with AD and has pharmacologic relevance is currently not known but worth investigation.

Proinflammatory cytokines, such as IL-1, IL-6, and TNF-α, play a major role in psoriasis, but their functional role in AD is less well understood. Microarray data obtained from the skin of patients with psoriasis and AD show that both IL-1β and TNF-α are more highly expressed in patients with psoriasis compared with levels seen in patients with acute AD.[34] In line with this, therapeutic inhibitors of TNF-α are highly effective in psoriasis. Likely because of an inferior role for the inflammatory response in AD, pilot studies with TNF-α inhibitors in patients with AD were disappointing. Etanercept was only minimally effective in

2 children with AD,[35] and infliximab, although showing an initial response in most patients, was not effective over a period of 46 weeks in an open-label, noncontrolled study in 7 of 9 patients with severe AD.[36] We are not aware of clinical studies in AD using anakinra, the recombinant form of the IL-1 receptor antagonist.

The hygiene hypothesis, reviewed in detail elsewhere,[37-39] implies that a deficiency of environmental stimuli to activate the innate immune system resulting in a strong $T_H1$ response in early childhood favors instead the induction of a proallergic $T_H2$ pathway. This should ultimately lead to infant AD as the first step in the cascade of atopic diseases, followed then by allergic asthma and rhinitis (the atopic march). As a consequence of this concept, many researchers have started investigating therapeutic strategies to improve an early $T_H1$ response (ie, by administering probiotics to pregnant women and subsequently during the first months of life to the newborns at risk of atopy later in life). In this way the onset of AD should be prevented. This treatment strategy should be also effective even when AD is already established in infancy. A recent meta-analysis[40] and an in-depth review of the most recent literature[41] addressing the question of the effect of probiotics for the prevention and treatment of infant AD did not conclude with an unambiguous recommendation. Since then, 2 more studies were published. Kopp et al[42] essentially repeated the initial randomized controlled study conducted by Kalliomaki et al[43-45] that had shown a prevention of the onset of AD in infants by 50% versus placebo during follow-up periods of 2, 4, and 7 years and, surprisingly enough, came to different results. The second study was a controlled intervention study in 3- to 12-month-old infants with AD and evaluated a 12-week probiotic food supplementation versus placebo.[46] No clinical treatment effect over that seen with placebo was observed.

Although most studies used the probiotic strain *Lactobacillus rhamnosus* GG (ATCC 53103) and can therefore be compared with each other, there might still be differences in the various study protocols, substantially affecting the results. Should this indeed be the case, these differences need to be understood for the conduct of a new series of controlled trials before a clear recommendation can be given as to whether probiotic treatment or prevention is a meaningful therapy.

A second vehicle to promote a $T_H1$ response in atopic infants is the killed strain *Mycobacterium vaccae* (SRL 172), which has been shown to be effective in a number of small trials in the improvement of disease severity when administered intradermally.[47,48] A recently published randomized controlled study investigating the therapeutic value of *M vaccae* in the treatment of school-aged children with moderate-to-severe AD could not establish a treatment effect over that seen with placebo after 12 weeks.[49] Again, this study leaves a number of questions open related to the applicability of the hygiene hypothesis to treat AD.

## THE ROLE OF ADAPTIVE IMMUNITY IN AD PATHOGENESIS

As already mentioned above, a $T_H2$-dominated cytokine milieu downregulates the antimicrobial peptidic response in AD skin[22] and FLG expression in keratinocytes,[18] demonstrating how much innate and adaptive immune responses can be linked to the skin barrier function. Therapeutic concepts targeting the $T_H2$ response might therefore have a positive effect on components of both the innate immune response and the epidermal barrier. Unfortunately, the clinical relevance of the hypothesized $T_H2$ response in AD is still unclear. Although a soluble form of the IL-4 receptor has been tested as an inhalative agent for extrinsic asthma,[50,51] no reports are available demonstrating its use or efficacy in AD. Also, we are not aware of any trials in AD testing antibodies directed against IL-13. Preliminary experience with the anti-IL-5 antibody mepolizumab suggests that it significantly reduces blood and skin eosinophil numbers but neither inhibits an atopy patch test or a late-phase skin reaction nor induces a satisfying clinical response in patients with AD.[52-54] Because mepolizumab did not show an effect on T-cell cytokine production in patients with asthma,[55] it can be argued that a strong effect on eosinophils in the absence of any immunoregulatory activity on T cells is not sufficient to improve AD disease severity.

This highlights the importance of T cells for the skin infiltrate. In fact, biologic therapies targeting predominantly T cells, such as efalizumab and alefacept, both approved for the treatment of psoriasis, have been shown to be somewhat effective in AD. Alefacept, a leukocyte function antigen 3/Ig fusion protein targeting CD2 on T cells, showed a significant reduction of Eczema Area and Severity Index scores in 10 patients with moderate-to-severe AD over 12 weeks of treatment in an open-label study.[56] Production of IL-4, IL-5, IL-13, and IFN-γ by *ex vivo* stimulated T cells from blood decreased during treatment, as did mRNA levels for IL-5, IL-13, and IL-10 in the skin. Moul et al[57] reported on 9 patients treated for 16 weeks with alefacept. Although there was a trend toward clinical improvement in the majority of the patients, the results were less conclusive. Efalizumab, an anti–leukocyte function antigen 1 (CD11a) antibody, has been tested in an open-label proof-of-concept trial in 10 patients with severe AD.[58] A highly significant mean improvement of clinical severity was observed within 12 weeks of treatment. Other case reports support this observation,[59-61] and Harper et al[62] found strong evidence of inhibition of T-cell extravasation from the blood into the skin in 10 patients treated with efalizumab. Overall, these initial data validate the hypothesis that activated T cells in the skin are necessary for the clinical phenotype of AD and warrant randomized controlled studies to confirm the value both alefacept and efalizumab might have for the treatment of severe AD.

Exoallergens, such as house dust mite and pollens, are certainly of critical importance for the initiation of an adaptive immune response, but there might also be a role for autoantigens in the perpetuation of skin lesions.[63,64] This leads to the question of the role of B cells, IgE, and allergens presented by DCs for the pathogenesis of AD.

The anti-CD20 antibody rituximab, approved for the treatment of rheumatoid arthritis, showed impressive improvement of clinical severity in 6 patients with severe AD within 4 to 8 weeks associated with a reduction of blood and skin B cells by 50% and a reduction of IL-5– and IL-13–producing skin cells.[65] However, this finding was not confirmed in another study in which rituximab was administered to 2 patients with severe AD.[66] Although more investigation is certainly required to prove this concept, these preliminary data suggest that there might be indeed a role for B cells in AD, perhaps in their role as antigen-presenting cells for memory responses.

High total IgE levels, suspected to be the result of an unbalanced $T_H2$ response *in vivo*, are a hallmark of extrinsic AD, but their role in the pathogenesis of AD remains unknown or speculative in the absence of well-designed trials targeting IgE. The

anti-IgE antibody omalizumab, approved for the treatment of extrinsic asthma, should be a perfect tool to study the role of IgE in AD. In fact, one of the authors (G.S.) observed that omalizumab, when administered to patients with AD, can displace IgE not only from basophils and mast cells but also from DC surfaces in peripheral blood and skin. The results of the few small clinical trials conducted thus far are controversial to say the least. Krathen and Hsu[67] reported 3 patients with severe AD and excessive levels of total IgE (>5000 IU/mL) not responding to omalizumab, whereas Lane et al[68] described 3 patients who responded well when omalizumab was administered as an add-on therapy. In another case series, 7 patients severely affected with AD were treated with omalizumab, and 5 of 7 achieved a clinically meaningful improvement[69] within 8 to 12 weeks of treatment. Belloni et al[70] studied 11 patients and found no improvement or even a deterioration in 5 of 11 of them, and in 6 of 11 they found a very good or satisfying clinical response. Although omalizumab is indicated for the treatment of asthma when IgE levels do not exceed 700 IU/mL, it was hypothesized that it was not effective in severe AD because IgE levels in the studied patients were much higher than 700 IU/mL.[71] Whether this explains the controversial data observed in patents with AD remains currently open.

In view of the fact that different pathogenetic principles might be operative in various forms of the disease (acute vs chronic, adult vs child), the possibility exists that a possible beneficial effect of anti-IgE treatment on a particular subgroup might have been overlooked. More extended and randomized controlled studies considering this aspect might be helpful in resolving this open issue.

Interestingly, omalizumab had an effect on the late-phase skin reaction mediated by a clinically relevant allergen in allergic individuals.[72] It inhibited the size of the cutaneous reaction and abrogated the influx of T cells, eosinophils, neutrophils, and mast cells triggered by the intradermal injection of the allergen. This suggests that omalizumab might be effective under conditions in which allergens exacerbate the clinical course of the disease. Thus the reduction of specific IgE levels in subjects allergic to a clinically relevant allergen might be a therapeutic option. Specific immunotherapy aims to achieve this and should therefore improve clinical symptoms in those patients with AD in whom an allergen could be identified as a disease-confounding factor. This concept is not new; however, systematic and controlled data are sparse, as reviewed by Bussmann et al.[73] A recently published open-label study indicated that subcutaneous immunotherapy with a house dust mite allergoid in 25 subjects with AD improved clinical severity within 4 weeks, which was associated with a decrease of allergen-specific IgE levels.[74] Werfel et al[75] conducted a dose range–finding study with house dust mite allergen over 1 year and observed a treatment benefit over baseline with the 2 highest doses. In addition, a randomized controlled study with sublingual house dust mite immunotherapy showed that active intervention was associated with a better clinical improvement in mild-to-moderate AD after 3 months compared with that seen with placebo.[76] Moreover, the question of whether a perinatal and early-in-life avoidance of potential allergens in high-risk children would have a benefit in the occurrence and severity of AD later in childhood was addressed in a recently published study by Arshad et al.[77] In this controlled study children were randomized to a cohort in which exposure to food and house dust mite was reduced versus a standard-of-care control group. Children were followed up for 8 years, and data indicate that active intervention significantly reduced the risk of AD during childhood. Thus these new controlled trials suggest that allergen avoidance or allergen immunotherapy can be effective and suggest a role of house dust mite for the appearance and severity of AD. Further controlled studies with more subjects confirming these data in addition to long-term data on the outcome of AD after cessation of the therapeutic intervention are certainly needed.

These principles applying for house dust mite allergens might be true also for clinically relevant food allergens in sensitized children with AD. In general, food allergies are outgrown because of naturally occurring tolerance mechanisms that are only partially understood. Specific IgE to the food allergen shows prognostic value. Boyano-Martinez et al[78] studied the time to tolerance in a cohort of 2-year-old children allergic to egg. Although the median time from the first reaction after eating egg to tolerance was 27 months in children with low levels of egg-specific IgE, it was 59 months among those with high levels of specific IgE. Thus it can be speculated as to whether attempts to reduce specific IgE levels by means of immunotherapy or even by means of transient treatment with omalizumab or an anti-IL-4 antibody would accelerate tolerance induction. The conduct of such proof-of-concept trials would of course not be trivial given the young age of these patients.

A matter of debate is the nature of the pathophysiologically relevant antigen-presenting cell or cells. It appears that both Langerhans cells and inflammatory DCs are important in this regard. Although the former probably contribute to the $T_H2$ polarization seen in acute skin lesions, the latter seem to be responsible for skewing the immune response in the $T_H1$ direction.[79] In AD skin lesions the majority of Langerhans cells and inflammatory DCs exhibit surface-bound IgE, with FcεR1 being the critical IgE-binding structure.[80] *In vitro* studies have demonstrated that ligation of FcεR1-bound IgE on dendritic antigen-presenting cells results in a greatly enhanced T-cell response[81] and in the production of chemotactic cytokines, such as IL-16.[82] The *in vivo* significance of these *in vitro* findings is questioned by clinical trials, with anti-IgE antibodies demonstrating no substantial clinical benefit in patients with AD.

As far as the quality of the T-cell response is concerned, the keratinocyte-derived IL-7–like cytokine thymic stromal lymphopoietin (TSLP) is critically needed for evoking a $T_H2$ response. It is greatly overexpressed in AD epidermis and signals DCs to drive $T_H2$ polarization[83] and to produce the $T_H2$ cell–attracting thymus and activation-regulated chemokine. Interestingly enough, recent evidence exists that eosinophil- and basophil-derived IL-25, a distinct member of the IL-17 cytokine family, enhances the expansion and functions of TSLP-DC–activated $T_H2$ memory cells, thus augmenting allergic tissue inflammation.[84] In keeping with these observations is the finding of substantial numbers of $T_H17$ cells in acute, but not chronic, AD lesions,[85,86] indicating that IL-17 and IL-22 play important roles in the emergence of acute AD skin lesions. Thus targeting TSLP or IL-17 might be a potential new treatment option for patients with AD.

The factors responsible for the switch from a $T_H2/T_H17$- to a $T_H1$-dominated allergic tissue response are not fully understood. Novak et al[79] have shown that FcεR1 engagement of inflammatory DCs induces them to produce the $T_H1$-promoting cytokines IL-12 and IL-18. A role of TSLP in this switch has been implicated by Gilliet et al,[87] who reported that TSLP- and CD40 ligand–activated DCs induce IFN-γ–producing proallergic

**TABLE I.** Summary of potential new therapeutics for AD

| Compartment | Target | Therapeutic | (Potential) Outcome | Reference* |
|---|---|---|---|---|
| Skin barrier function | Lipids | Emollients | Moisturizing, reduced TEWL, reduced pruritus and inflammation | Chamlin et al[14] |
| | Proteases | Small inhibitory molecules, applied topically | Moisturizing, reduced TEWL, reduced pruritus and inflammation | |
| Innate immune system | Vitamin D receptor | Vitamin D3 | Increase of antimicrobial peptides | Katayama et al[32] |
| | Calcineurin | Calcineurin inhibitor | Increase of antimicrobial peptides | *In vitro*: Buchau et al[33] |
| | Proteases | Small inhibitory molecules, applied topically | Stabilization of antimicrobial peptides | NA |
| | DCs | Probiotics | Restoration of $T_H1/T_H2$ homeostasis | Conflicting results: Lee et al[40] |
| | Total IgE | Anti-IgE antibody omalizumab | Reduction of circulating IgE, reduced expression of FcεRI on mast cells, basophils, and DCs | Conflicting results: Beck and Saini[71] |
| | TNF-α | Anti–TNF-α antibody infliximab | Transient clinical improvement | Jacobi et al[36] |
| Adaptive immune system | T cells | Alefacept, efalizumab | Clinical improvement | Simon et al[56] and Takiguchi et al[58] |
| | B cells | Rituximab | Clinical improvement | Simon et al[65] |
| | Specific immunotherapy | House dust mite–specific T and B cells | Clinical improvement | Bussmann et al[74] and Werfel et al[75] |
| | TSLP, IL-4, IL-13, IL-17, IL-31 | Biologic? | Inhibition of $T_H2$ cells, reduction of pruritus, improvement of skin barrier function and expression of antimicrobial peptides | NA |

*TEWL*, Transepidermal water loss; *NA*, not available.
*Example references for application in patients with AD.

cytotoxic cells. Such cells have been implicated in the Fas-induced apoptosis of keratinocytes in eczematous dermatitis.[88]

The role, if any, of regulatory T cells in AD pathogenesis has yet to be determined. Reports exist that they are increased in the circulation but, perhaps as a consequence of exuberant amounts of bacterial superantigens, decreased in the skin of patients with AD.[89,90]

## OTHER ASPECTS

Dermal fibrosis is a salient feature of chronic AD lesions. There exists evidence that TGF-β and IL-11, mainly produced by eosinophils, are the major fibrogenic cytokines in chronic AD and that type I collagen is the major collagen subtype involved in this tissue-remodeling process.[85] We now know that vascular endothelial growth factor (VEGF) is massively overproduced in AD skin lesions, in particular the 121 isoform that exclusively induces hyperpermeability of blood vessels.[91] Downregulation of VEGF production or blockade of VEGF action might therefore be a promising new treatment strategy for AD. To the best of our knowledge, no clinical trials in AD targeting angiogenesis have been conducted or published yet. Although a wide variety of biologic response modifiers (eg, neuropeptides, proteases, and kinins) can induce pruritis, the nature of the pathophysiologically relevant itch mediator has remained enigmatic.[92] It now appears that the $T_H2$ cytokine IL-31 could be a major factor in this regard.[93] It is significantly overexpressed in pruritic versus nonpruritic AD skin lesions and in leukocytes from atopic individuals compared with those from healthy control subjects. Its receptor is abundantly expressed in dorsal root ganglia (ie, the site where the cell bodies of cutaneous sensory neurons reside).

IL-31 also induces several chemokine genes[94] and might therefore also play a role in the perpetuation of atopic skin inflammation. Another promising candidate potentially mediating pruritus in AD is kallikrein 7,[10] which also plays a role for the epidermal barrier function, as described above. The cannabinoid receptor on keratinocytes seems to be a target for both itch and skin inflammation, at least in an animal model.[95] Although this list of potential pruritic mediators is not complete, it shows that pruritus cause might be closely linked to the barrier function and the innate/adaptive immune system in patients with AD.

The safety and efficacy of classical immunosuppressive drugs in patients with severe AD has been continuously studied over the last few years. Although methotrexate is widely prescribed for the treatment of psoriasis and rheumatoid arthritis, it is rarely used for severe AD. A recent open-label, dose-escalating study in 12 adult patients with severe AD demonstrated a 52% improvement in the clinical score over baseline values at week 24, and only 1 patient withdrew from further treatment because of adverse events, a result that is clinically meaningful.[96] By using the same scoring

system (six-area, six-sign SD score), azathioprine showed a 37% improvement over baseline values at week 12 (placebo 20%) in a double-blind, placebo-controlled study in patients with moderate-to-severe AD older than 16 years,[97] thus confirming efficacy as assessed during an earlier trial.[98] Although adverse events, such as leucopenia and increased liver transaminase levels, need to be carefully monitored, these data indicate that azathioprine is effective in AD. Mycophenolate mofetil (MMF) has been studied in adults and children with severe AD in an open-label way. Of 14 children treated with MMF, only 1 did not respond well.[99] Furthermore, in a case series of 20 adult patients, only 3 showed no clinical response.[100] Although there are no randomized controlled trials published, these data indicate that MMF can be an effective treatment for patients with severe AD. Conversely, initial encouraging reports with montelukast, a specific cysleukotriene receptor antagonist approved for the treatment of asthma and allergic rhinitis, for the treatment of AD could not be confirmed in a recently published randomized controlled study.[101] Within a treatment period of 8 weeks, there was no evidence of a treatment effect of montelukast over placebo.

## CONCLUSION

The concept of epidermal barrier dysfunction as a major contributor to the pathogenesis of AD has experienced a renaissance over the last years. Some investigators believe that this defect is the primary event in disease pathogenesis, allowing the entrance of large immunogenic protein antigens in the epidermis/skin. A restoration of the barrier function by supplementing lipids or inhibiting proteases seems a feasible and promising approach, even if an important structural protein, such as FLG, is missing. New insights into the regulation of antimicrobial peptides in the epidermis suggest that vitamin D3 or calcineurin inhibitors could potentially stimulate the production of these peptides, perhaps even in a $T_H2$-dominated milieu. This is a testable hypothesis. Because a $T_H2$-dominated milieu might further impair the skin barrier function, as well as the innate immune system, in patients with AD, strategies to inhibit $T_H2$ cells are needed to address this issue. In the absence of specific biologics targeting $T_H2$ cells or cytokines, the latest results on immunotherapies with house dust mite allergens indicate that this could be a novel therapy for those patients in whom house dust mite seems to be a clinically relevant trigger.

Table I summarizes briefly the discussed therapeutic strategies. Despite this progress, the nonsatisfying situation is that many of the new discoveries and developments in AD research have not found adequate translation into meaningful proof-of-concept trials yet. Therefore the therapeutic armamentarium is still limited and far from being optimal. To fulfill the demand for more effective and safe therapies for moderate-to-severe AD, more basic research and faster translational science is required to overcome the hurdles of discovering and validating new targets, as well as conducting controlled studies with clinically meaningful end points.

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