Investigational and Unproven Therapies in Atopic Dermatitis

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• Atopic dermatitis • Treatment • Experimental therapy

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that affects up to 20% of children and 2% of adults worldwide in both developed and developing countries.[1] The significant effect of the disease on patients and their caregivers has been well documented[2,3] (see also the article by Chamlin and Chren elsewhere in this issue for further exploration of this topic), as has the economic effect on families and society.[4,5] Although patients with milder disease may respond to several conventional therapies, new therapeutic interventions are needed for those patients in whom the disease is difficult to control.

CONVENTIONAL THERAPY

AD is a complex disease with multifactorial causes, including skin barrier defects and immune dysregulation with irritant, allergic, and infectious triggers.[6–8] Avoidance of proven triggers (see the article by Caubet and Eigenmann elsewhere in this issue for further exploration of this topic), along with proper skin hydration and moisturization, forms the foundation of conventional therapy.[9] Topical corticosteroids (TCSs) remain the first-line anti-inflammatory therapy for symptomatic treatment of AD.[10] However, nonadherence in using TCSs remains an important barrier in the treatment of AD, with patients or caregivers often delaying use of the TCSs for up to 7 days after onset of flare.[11–13] Nonsteroidal medications include the topical calcineurin inhibitors (TCIs) pimecrolimus cream 1% (Elidel) and tacrolimus ointment 0.03% and 0.1% (Protopic). These medications are currently indicated as second-line treatment for intermittent, noncontinuous use in children aged 2 years and older with moderate to severe AD (tacrolimus ointment 0.03%) and mild to moderate AD (pimecrolimus cream 1%).

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Tacrolimus ointment 0.1% is indicated for patients 16 years and older. Despite well-documented safety,[14–16] their use significantly decreased after a boxed warning issued by the Food and Drug Administration (FDA) that long-term use may be associated with risk of cancer. Evolution in conventional therapy using a proactive approach with both TCSs and TCIs is reviewed by Wollenberg and Schnopp elsewhere in this issue. Newer nonsteroidal creams registered as medical devices, thus requiring a prescription despite not being FDA-regulated, include Atopiclair, Eletone, EpiCeram, and MimyX.[17] These creams have no age or length-of-use restrictions; however, they are expensive, and comparison with topical treatments has been limited.[18]

For patients with severe AD, systemic immunosuppressive drugs, including cyclosporine, mycophenolate mofetil, azathioprine, and methotrexate, have been shown to be effective, although serious adverse events limit their use, especially in pediatric patients.[10,19] Other approaches include ultraviolet (UV) phototherapy[20] and wet-wrap therapy.[21] The latter may be especially effective when incorporated into a comprehensive management program.[22] An important clinical point is that successful outcomes in the management of patients with AD are strongly tied to proper education of patients and caregivers (see the article by Nicol and Ersser elsewhere in this issue for further exploration of this topic).

INVESTIGATIONAL OR UNPROVEN THERAPIES

Barrier Therapy

The goal of barrier therapy in AD is to repair an abnormal epidermal barrier and prevent barrier dysfunction.[23] Loss-of-function mutations in the filaggrin gene have been shown to be associated with reduced levels of natural moisturizing factor in the stratum corneum.[24] In a recent randomized, controlled, prospective study, Wirén and colleagues[25] showed that a barrier-strengthening cream containing urea (Canoderm cream 5%) was capable of delaying the relapse of AD in patients who had been treated with TCSs. The subjects were first treated with betamethasone valerate cream 0.1% on defined areas of eczema for 3 weeks; they were then randomized to receive Canoderm or no treatment. Over a 6-month period, 68% of the treated group had no relapse of eczema versus 32% of the untreated group ($P<.01$). However, skin barrier function, as measured by transepidermal water loss (TEWL), was not significantly different between the 2 groups. The study highlights the importance of barrier treatment in the prevention of symptoms in established AD. However, larger studies and comparison with other barrier treatments are needed to confirm these results.

A study of extracts prepared from silica mud and 2 different microalgae species derived from a specific geothermal biotope in Iceland known to be beneficial for patients with AD showed them to be capable of inducing filaggrin and other epidermal barrier gene expression in primary human epidermal keratinocytes.[26] In addition, a formulation containing all 3 extracts induced identical gene regulatory effects in vivo, associated with a significant reduction of TEWL when applied topically to normal skin in healthy subjects.

Antistaphylococcal Treatments

Because *Staphylococcus aureus* appears to play an important role in the pathogenesis of AD inflammation,[8] strategies to decrease colonization and neutralize effects of superantigenic toxins with superantigenic properties would be especially important. The emergence of methicillin-resistant *S aureus* (MRSA) as an increasingly common pathogen in patients with AD underscores the urgency of developing new treatments in this area.[27]

Antimicrobial fabrics

Silver- or antimicrobial-coated fabrics have been found to be effective in the treatment of AD.[17] More recently, in an explorative 8-week study, Fluhr and colleagues[28] showed that silver-loaded seaweed fiber clothing significantly decreased *S aureus* colonization in patients with AD compared with cotton garments. In addition, the group with silver-loaded seaweed fiber clothing had significant improvement in their skin barrier function in areas of mild eczema during the initial 4 weeks of treatment as compared with the cotton fiber group. The investigators hypothesized that an antioxidative effect of the silver-loaded seaweed fiber contributed to clinical benefit. Of note, they showed that there was no deleterious effect of the active treatment on commensal bacteria. This observation may be of clinical importance, given recent data that showed that *Staphylococcus epidermidis* may play a beneficial anti-inflammatory role in cutaneous inflammation.[29] Further studies are needed to compare the clinical improvement of AD and potential side effects using these fabrics.

Bleach baths

Huang and colleagues[30] confirmed the efficacy of bleach bath in AD in a randomized, investigator-blinded, placebo-controlled study. In this pediatric study, 15 children with AD were randomized to treatment with diluted bleach (0.005%) twice weekly along with nasal mupirocin added for 5 days each month versus 16 patients with AD treated with water twice weekly and application of nasal petrolatum. After 3 months, AD severity based on the eczema area and severity index (EASI), body surface area involved, and Investigator's Global Assessment improved significantly in the bleach bath–treated group. Of note, there was no significant difference in the AD severity on body parts (head and neck) that were not submerged in the bleach bath. There were no significant adverse events noted, and no patients withdrew from the study because of their intolerance to the baths. This treatment might be especially useful for patients with recurrent MRSA infections. Unfortunately, this study did not address this question and, in addition, patients on active treatment remained colonized by *S aureus*. It is worth noting that many patients with AD, especially those with open and inflamed lesions, do not tolerate even dilute bleach baths.

Topical antiseptics

Topical antiseptics remain an attractive antistaphylococcal treatment for AD because of their low risk of causing bacterial resistance. However, a well-known side effect of antiseptics is their potential for causing local irritation or sensitivity. In a double-blind randomized study, Wohlrab and colleagues[31] used a combination of 2 topical antiseptics, triclosan 0.3% and chlorhexidine 0.34%, in lower concentrations in a carrier emulsion for topical treatment of AD and compared it to topical triclosan 2% in the same carrier emulsion. These investigators found that the low-concentration combination therapy led to a similar reduction in AD severity as the higher-concentration single antiseptic at a 2-week follow-up, with a similar reduction in bacterial counts. However, comparison of adverse events was not reported.

In a more recent randomized, double-blind controlled trial, Tan and colleagues[32] showed that an emollient containing 1% triclosan had TCS-sparing effects in patients with mild to moderate AD compared with the emollient alone. Patients applied either the emollient alone or emollient with 1% triclosan on the whole body twice daily for 27 days. Both groups were allowed to apply betamethasone valerate cream 0.025% on the affected areas. The investigators had a follow-up on days 14, 27, and 41. AD severity measured by the scoring atopic dermatitis (SCORAD) index significantly improved on day 14 in the group using triclosan compared with the group using

only emollient. AD severity continued to improve in both groups, and there was no significant difference in AD severity between them on days 27 and 41. However, there was significantly less use of TCSs in the group taking triclosan than in the group taking only emollient over the 41-day study period ($P<.05$). Three subjects in the triclosan group experienced local stinging pain after application of the topical preparation compared with none in the emollient group. The stinging pain, however, resolved with continued use of the cream, and no subject withdrew from the study as a result of any an adverse effects.

Specific antibodies and vaccines

Community acquired (CA)-MRSA infections have become increasingly common among patients with AD.[27] An important virulence regulator in staphylococci that characterizes CA-MRSA strains is the accessory gene regulator agr.[33] Agr signals through an exported autoinducing peptide (AIP), and antibodies designed against the AIP of one *S aureus agr* subgroup have been shown to specifically prevent agr expression and *S aureus* disease in an animal model of abscess formation.[34] Of note, these antibodies also provided protection when administered before infection.

Devising new therapeutic strategies to combat *S aureus* is complicated by the infection not being associated with the development of protective immunity to any significant degree, partly because our immune system has ongoing exposure to staphylococcal antigens and many strains are commensal organisms. In addition, *S aureus* produces protein A to help it evade acquired host defense. Although several attempts to develop protective vaccines have met with failure in clinical trials, a new conjugated vaccine (PentaStaph) that includes α-toxin and Panton-Valentine leukocidin is currently in clinical trials. In addition, positive results based on using a combination of systematically selected antigens have been reported.[35] These combinatory vaccines target microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), a family of bacterial proteins that bind to human extracellular matrix components. Stranger-Jones and colleagues[36] developed a vaccine based on a combination of antigens that provided complete protection from lethal doses of *S aureus* in a murine challenge model. Of importance, MSCRAMM vaccines have been shown to prevent colonization.[37] Their clinical benefit in patients with AD remains to be determined.

Another promising antigenic target for vaccine development against *S aureus* is teichoic acid, which has been implicated in nasal colonization and biofilm formation.[38] In a recent study of children with impetiginized AD, significant levels of lipoteichoic acid were measured in infected lesions, which were able to induce epidermal cytokine gene expression ex vivo.[39]

Antistaphylococcal toxin strategies

Ultimately, treatment may need to be directed at eliminating or neutralizing exotoxins secreted by *S aureus* that contribute to the chronic inflammation and severity of AD.[7] Initial attempts at neutralizing staphylococcal enterotoxin B (SEB) with soluble high-affinity receptor antagonists appear to be promising.[40] Of importance, this group was also able to express Vβ domains in tandem as a single-chain protein demonstrating the feasibility of engineering a broader spectrum antagonist capable of neutralizing multiple toxins, including the clinically important superantigens, SEB and toxic shock syndrome toxin 1.[41]

Ceragenins

Besides problems with *S aureus*, patients with AD, even those with quiescent disease, have a unique susceptibility to eczema vaccinatum.[42] This potentially lethal reaction to

immunization with smallpox vaccine (vaccinia virus [VV]) may be related to a deficiency of antimicrobial peptides (AMPs).[43] Although cathelicidins and human β-defensin 3 exhibit potent antiviral activity against VV,[44] their use as anti-VV agents is limited because of rapid degradation by endogenous tissue proteases. Ceragenins are synthetic antimicrobial compounds designed to mimic the structure and function of endogenous AMPs.[45] Ceragenins have been shown to disrupt bacterial membranes without damaging mammalian cell membranes.[46] As a result of their synthetic nature, ceragenins are not subject to human protease degradation and therefore have a longer tissue half-life. One ceragenin compound (cationic steroid antimicrobial [CSA] 13) was recently shown to exhibit potent antiviral activity against VV via direct antiviral effects and by stimulating the expression of endogenous AMPs with known antiviral activity.[47] In addition, topical application of CSA-13 resulted in reduced satellite lesion formation, suggesting the use of CSA-13 as an acute intervention for patients with disseminated VV skin infection.

Anti-Inflammatory Therapies and Immunomodulation

Chemokine antagonists

An important role for chemokines in the pathogenesis of AD has emerged.[48] Increased levels of CCL17 and CCL22 have consistently been shown to correlate with increased severity or disease activity of AD.[49] Both CCL17 and CCL22 bind to CCR4 receptor to exert their chemotactic effects on leukocytes, and blocking CCR4 presents an opportunity to antagonize the action of these 2 chemokines. Nakagami and colleagues[50] showed that the novel compound RS-1154 competed with CCL17 in binding to human CCR4. In a mouse model, the investigators demonstrated that orally administered RS-1154 was capable of inhibiting ovalbumin-induced ear swelling caused by CCL17 and CCL22. CCR3 is another chemokine receptor that mediates allergic inflammation.[51] Suzuki and colleagues[52] found that the CCR3 antagonist YM-344031 significantly decreased ovalbumin-induced murine ear edema compared with vehicle. The anti-inflammatory effect of YM-344031 was similar to that of prednisolone. Taken together, these animal studies illustrate the potential value of chemokine antagonists for future human trials in the treatment of AD.

Transcription factor decoy oligodeoxynucleotides

Transcription factors are essential intracellular molecules in the inflammatory pathways. In murine models of AD, a topical decoy oligodeoxynucleotide (ODN) has been used to block NF-κB, a key transcription factor in inflammation.[17] More recently, Igawa and colleagues[53] conducted an open-label pilot study using topical decoy ODN ointment to block STAT6, a transcription factor critical in allergic inflammation, in 10 adult patients with moderate to severe AD. Each subject applied the topical STAT6 decoy ODN ointment to one side, with paired lesions treated with a control emollient. Both the EASI scores and visual analog scale (VAS), a measure of pruritus, decreased significantly on the side receiving active treatment at the 2- and 4-week visits ($P<.05$).

Interleukin-4 and interleukin-13 antagonists

Interleukin (IL)-4 and IL-13 are T-cell–derived cytokines that play an important role in acute AD.[7] Aeroderm, an IL-4 mutein, interferes with the IL-4α receptor, blocking both IL-4 and IL-13. In a randomized, double-blind, placebo-controlled trial of adult patients with moderate to severe AD, the drug was given twice daily for 28 days by subcutaneous injection.[54] Although the group treated with Aeroderm showed greater reduction in disease severity versus the placebo group, this was not a statistically significant difference. However, the active treatment group did have statistically significant decrease in eczema exacerbations. More recently, Morioka and colleagues[55] studied

the effect of murine IL-4 double mutant (DM), an IL-4 antagonist DNA capable of inhibiting the activity of IL-4 and IL-13. IL-4DM significantly suppressed oxazolone-induced ear swelling and dermatitis in the mouse model of AD compared with the control DNA-treated group. The group treated with IL-4DM also had significantly lower plasma IgE and histamine than the control group.

Suplatast tosilate

Suplatast tosilate is a Th2 cytokine inhibitor. Systemic administration of suplatast tosilate has been shown to be beneficial in AD.[56] In addition, topical therapy with suplatast tosilate ointment 3% inhibits the expression of IL-4 and IL-5 and ameliorates skin manifestations in a murine model of AD, suggesting potential usefulness for the treatment of AD.[57] A meta-analysis showed that suplatast/tacrolimus combination therapy resulted in better improvement in skin symptom scores and significantly decreased the dose of tacrolimus compared with topical tacrolimus alone.[58] In addition, a significantly greater number of patients were able to discontinue tacrolimus ointment by using the combination therapy with suplatast tosilate versus tacrolimus monotherapy for refractory facial erythema.

Peroxisome proliferator–activated receptor agonists

Peroxisome proliferator–activated receptors (PPARs) are nuclear hormone receptors that are expressed in a variety of cells, including keratinocytes and cells of the immune system that have potential anti-inflammatory activity and function in epidermal repair. In a retrospective review of 6 patients with severe AD, Behshad and colleagues[59] found that orally administered rosiglitazone, a PPAR-γ agonist approved for use in type 2 diabetes mellitus, significantly improved severity of AD when used concomitantly with oral corticosteroid or wet-wrap treatment in some subjects. Rosiglitazone had steroid-sparing effects in patients with severe AD. The dosage used ranged from 2 to 4 mg twice daily for up to 2 years. A significant side effect observed in the study was weight gain, although other potential side effects included edema, cardiovascular risk, and hepatotoxicity. Two more recent studies using PPAR agonists were done in mouse models of AD. The topically applied PPAR-α agonist WY14643 significantly decreased cutaneous inflammation accompanied by decreased infiltration of CD4 cells, mast cells, and eosinophils and decreased levels of the inflammatory cytokines IL-1β, IL-31, IL-4, interferon (IFN)-γ, and CCL11.[60] In another study, Hatano and colleagues[61] showed that topically applied agonists of PPAR-α, PPAR-β/δ, and liver X receptor–α/β significantly reduced epidermal hyperplasia and inflammation. These investigators also found that these agonists led to significant reduction in TEWL, cutaneous infiltration of eosinophils and mast cells, serum CCL17, and systemic Th2 cells. However, they could not confirm the effectiveness of a PPAR-γ agonist in this mouse model. A role for PPAR agonists in AD remains to be fully defined.

RDP58

RDP58 is a novel immunomodulating decapeptide discovered through activity-based screening and computer-aided rational design.[62] It disrupts cellular responses signaled through the toll-like and tumor necrosis factor (TNF) receptor families and occludes important signal transduction pathways involved in inflammation, inhibiting the production of TNF-α, IFN-γ, IL-2, IL-6, and IL-12. These proinflammatory cytokines are thought to be involved in the pathogenesis of several inflammatory and autoimmune diseases, including AD. Topical application of RDP58 to the epidermis resulted in amelioration of phorbol ester–induced irritant dermatitis.[62] Substantial reductions were observed in skin thickness, inflammatory cytokine production, and other histopathological parameters. RDP58 was also effective in reducing the

compounding inflammatory damage brought on by chronic 12-*O*-tetradecanoylphorbol 13-acetate exposure, and was capable of targeting inflammatory mediators specifically in keratinocytes. These results suggest that topical RDP58 is an effective anti-inflammatory agent with therapeutic potential in immune-mediated cutaneous diseases such as AD.

Intravenous immunoglobulin

High-dose intravenous immunoglobulin (IVIG) has been shown to have immunomodulatory activity in AD and, in addition, IVIG can interact directly with microbes or toxins involved in the pathogenesis of AD. IVIG has been shown to contain high concentrations of staphylococcal toxin-specific antibodies that inhibit the in vitro activation of T cells by staphylococcal toxins.[63] Treatment of severe refractory AD with IVIG has yielded conflicting results. Studies have not been controlled and have involved small numbers of patients.[64] Although children appear to have a better response than adults, controlled studies are needed to answer the question of efficacy in a more definitive manner.

Omalizumab

Anti-inflammatory effects of monoclonal anti-IgE suggest a role for IgE in allergic inflammation.[65] Several case reports suggest there are clinical benefits of using omalizumab (monoclonal anti-IgE) in some patients with AD, including children treated for their asthma.[66] Treatment of adult patients with severe AD and significantly elevated serum IgE levels did not show benefit when omalizumab was used as monotherapy.[67] By contrast, significant improvement in 3 adolescent patients with AD was observed when omalizumab was added to usual therapy.[68] In an open study of 11 adult patients with high IgE levels treated with anti-IgE, some patients had very good clinical improvement, others had none, and several had worsening of AD based on change in SCORAD.[69] Specific markers have not been found to identify potential responders, and at present the use of omalizumab is not indicated for AD.

Allergen-specific immunotherapy

Specific immunotherapy with aeroallergens is currently not indicated for AD. Although there are anecdotal reports of disease improvement, some patients also report exacerbations of eczema. More recently, Werfel and colleagues[70] showed that in adults with long-standing AD sensitized to dust mite allergen, specific immunotherapy with house dust mite allergen over 12 months resulted in clinical improvement and reduction in topical steroid use. In patients with AD having clinical improvement with subcutaneous allergen-specific immunotherapy (SCIT), Bussmann and colleagues[71] showed that levels of the tolerogenic cytokine IL-10 increased, whereas CCL17 and IL-16 decreased in the sera of the patients during SCIT. Allergen-specific IgE decreased whereas IgG4 increased during SCIT. Preliminary studies with sublingual immunotherapy suggest a role for a subset of children with AD sensitized to dust mite allergen.[72] These data need to be reproduced in a larger pediatric population, especially in light of the natural history of AD.

Vitamin D and heliotherapy

Use of topical vitamin D in AD has been controversial. In a mouse model of IgE-mediated cutaneous reactions, Katayama and colleagues[73] showed that a topical vitamin D_3 ointment was capable of inhibiting both immediate- and late-phase hypersensitivity reactions in the mouse model. However, in a different murine model, Li and colleagues[74] showed that topical application of vitamin D_3 or its analogue, calcipotriol (MC903; Dovonex), increased the production of thymic stromal lymphopoietin,

a cytokine associated with Th2 responses and IgE production, and led to the development of eczematous changes. The investigators observed increased pruritus, epidermal hyperplasia, and increased numbers of cutaneous eosinophils and systemic IgE, similar to findings in patients with AD.

The skin is crucial for synthesizing vitamin D after exposure to sunlight. Because people in Scandinavia have limited exposure to sunlight in the winter and are at risk for seasonal vitamin D insufficiency, a group of Finnish researchers hypothesized that heliotherapy may lead to increased vitamin D production and improvement of AD during the winter.[75] Their study included 23 adult patients with AD who received heliotherapy for 2 weeks either in January or March in the Canary Islands. The investigators showed that both groups had significantly increased serum concentration of calcidiol, the circulating form of vitamin D, after heliotherapy. Both groups had significant improvement of AD severity based on a decrease in SCORAD after heliotherapy. In addition, there was a positive correlation in the improvement of serum calcidiol concentration and SCORAD in the group receiving heliotherapy in March. The improvement of AD after heliotherapy shown in this study was consistent with another study[76] and provided indirect support for the beneficial effect of vitamin D in AD. However, benefits need to be weighed against potential long-term adverse effects of heliotherapy, including the development of skin cancer. To improve winter-related AD without exposure to potentially harmful UV radiation, a pilot randomized, double-blind placebo-controlled study was performed with oral supplementation of vitamin D from February to March in Boston, Masachussets.[77] Eleven pediatric patients with mostly mild AD were enrolled. Subjects were assigned to take either vitamin D (1000 international unit [IU] ergocalciferol) or placebo once daily for a month. The Investigator's Global Assessment score improved in 4 of 6 subjects in the group taking vitamin D (80%) compared with 1 of 5 subjects in the group taking placebo ($P = .04$). There was a larger reduction in EASI score of the vitamin D group compared with the placebo group, but the difference was not statistically significant.

Cutaneous lesions in patients with AD have significantly decreased expression of AMPs compared with psoriatic lesions.[78] This decreased expression may contribute to increased *S aureus* infections observed in AD compared with psoriasis.[79] In a controlled study, 14 healthy subjects and 14 subjects with AD were supplemented with 4000 IU per day of oral vitamin D_3 (cholecalciferol) for 3 weeks.[80] Expression of the AMP cathelicidin was significantly increased in the skin biopsy specimens of AD lesions compared with those in healthy skin or uninvolved skin in AD. Although the study did not document changes in AD severity or bacterial counts with this treatment, it has implications for a role of oral vitamin D in improving innate immune responses in patients with AD, leading to decreased skin infections and clinical improvement. Sponsored by National Institutes of Health, a multicenter trial of oral vitamin D supplementation is currently being conducted (see the article by Searing and Leung elsewhere in this issue for further exploration of this topic).

Mycobacterium vaccae vaccine

AD is characterized systemically by a predominant Th2 response. Thus, one treatment strategy involves the shifting of a Th2 to a Th1 response. Because mycobacterial infections are known to trigger Th1 responses, several studies have evaluated the efficacy of heat-killed *Mycobacterium vaccae* (HKMV) vaccination in the treatment of AD. In a randomized, double-blind, placebo-controlled trial involving children aged 5 to 18 years with moderate to severe AD, Arkwright and David[81] showed that a single-dose injection of HKMV (SRL172) significantly decreased involved areas and dermatitis score at a 3-month follow-up, whereas there was no significant change in the group

treated with placebo. In an attempt to replicate these results, 2 larger randomized, double-blind, placebo-controlled studies involving patients with AD of similar age range and disease severity using intradermal injection of HKMV or its derivative were performed. In one study, Berth-Jones and colleagues[82] found that a single intradermal injection of HKMV (SRP299) did not result in significant difference between the groups taking HKMV and placebo in affected surface areas, dermatitis score, or quality of life at a 3- or 6-month follow-up. More recently, Brothers and colleagues[83] used 3 intradermal injections of a derivative of HKMV (AVAC) at a biweekly interval. These investigators also found no significant difference between the groups in affected surface areas, dermatitis score, or quality of life at 3- and 6-month follow-up. In addition, in a younger age group (2–6 years) with moderate to severe AD, another double-blind, placebo-controlled study failed to confirm the efficacy of HKMV (SRP299).[84] Spontaneous improvement of AD was noted in both groups, consistent with the natural history of this disease.

Antipruritic Therapy

Opioid receptor antagonist

A double-blind, placebo-controlled trial of adult patients with AD using a topical naltrexone cream 1% showed that the cream had a significantly quicker onset of itch relief compared with placebo.[85] More recently, Malekzad and colleagues[86] showed that oral naltrexone significantly decreased itch, as measured by VAS, in a double-blind, placebo-controlled study of adult patients with AD. The subjects were given 25 mg of naltrexone or placebo capsules twice daily for 2 weeks, and VAS was measured at baseline, 1 week, and 2 weeks. There was no significant difference in VAS between the 2 groups at baseline, but the naltrexone group had significantly decreased VASs at 1 week and 2 weeks compared with the placebo ($P<.005$ and $P<.001$, respectively). Side effects in the group treated with naltrexone included dizziness, nausea, vomiting, headache, and cramps.

Selective serotonin reuptake inhibitors (SSRIs) have been proposed to have some effects on opioid receptors. In an open-label study involving 72 patients with pruritus of various conditions (of which only 3 subjects had AD), 2 SSRIs (paroxetine and fluvoxamine) had anti-itch effects in 68% of the patients.[87] Subjects with AD were among the subgroup of patients who had the best response. Further controlled studies specifically in patients with AD need to be conducted.

Anti–IL-31

IL-31 is produced primarily by Th2 cells and has been implicated in the pruritus associated with AD.[88] In a mouse model of AD, Grimstad and colleagues[89] showed that monoclonal anti–IL-31 antibody injection significantly decreased scratching behavior over a period of 7 weeks. The study illustrates the potential use of an IL-31 blocker as an antipruritic agent in AD, although studies need to be done in humans.

Semaphorin3A

In a study with skin biopsy specimens, Tominaga and colleagues[90] showed that there is decreased expression of semaphorin3A (Sema3A) and increased density of epidermal nerve fibers in the skin of patients with AD compared with that in healthy individuals. These investigators hypothesized that Sema3A may regulate the growth of nerve fibers that innervate the skin of patients with AD. In a murine model, Yamaguchi and colleagues[91] showed that injection of Sema3A significantly decreased the density of cutaneous nerve fibers, and led to decreased scratching behavior and improvement of eczematous changes. Recently, psoralen-UV-A (PUVA) therapy was shown to modulate Sema3A and nerve growth factor in patients with AD, decreasing

epidermal expression of nerve growth factor and increasing epidermal expression of Sema3A.[92] PUVA therapy in these patients led to decreased epidermal nerve density and VAS score, and clinical improvement of AD. Reciprocal expression of nerve growth factor and Sema3A and their correlation with AD symptoms suggests a potential therapeutic approach in treating the pruritus of AD by regulating the levels of these proteins.

SUMMARY

AD remains an important disease, and it cannot be controlled in all patients with conventional therapies. The reasons for this are complex and include difficulty avoiding triggers, lack of understanding of skin care, suboptimal adherence with prescribed medications, limitations of medications due to adverse effects, and inadequate response to prescribed therapy. New insights into the complex pathogenesis of AD will likely lead to more targeted treatment for this disease. Novel therapies will likely emerge based on our increasing understanding of unique phenotypes of AD. Of note, filaggrin mutations have been shown to predispose to allergic inflammation in a mouse model.[93] Future antimicrobial approaches in AD may involve modulation of AMP expression. Specific therapies directed at pruritus in AD that lack the adverse effects of current therapies are needed because these symptoms continue to affect the quality of life of patients and their families.

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