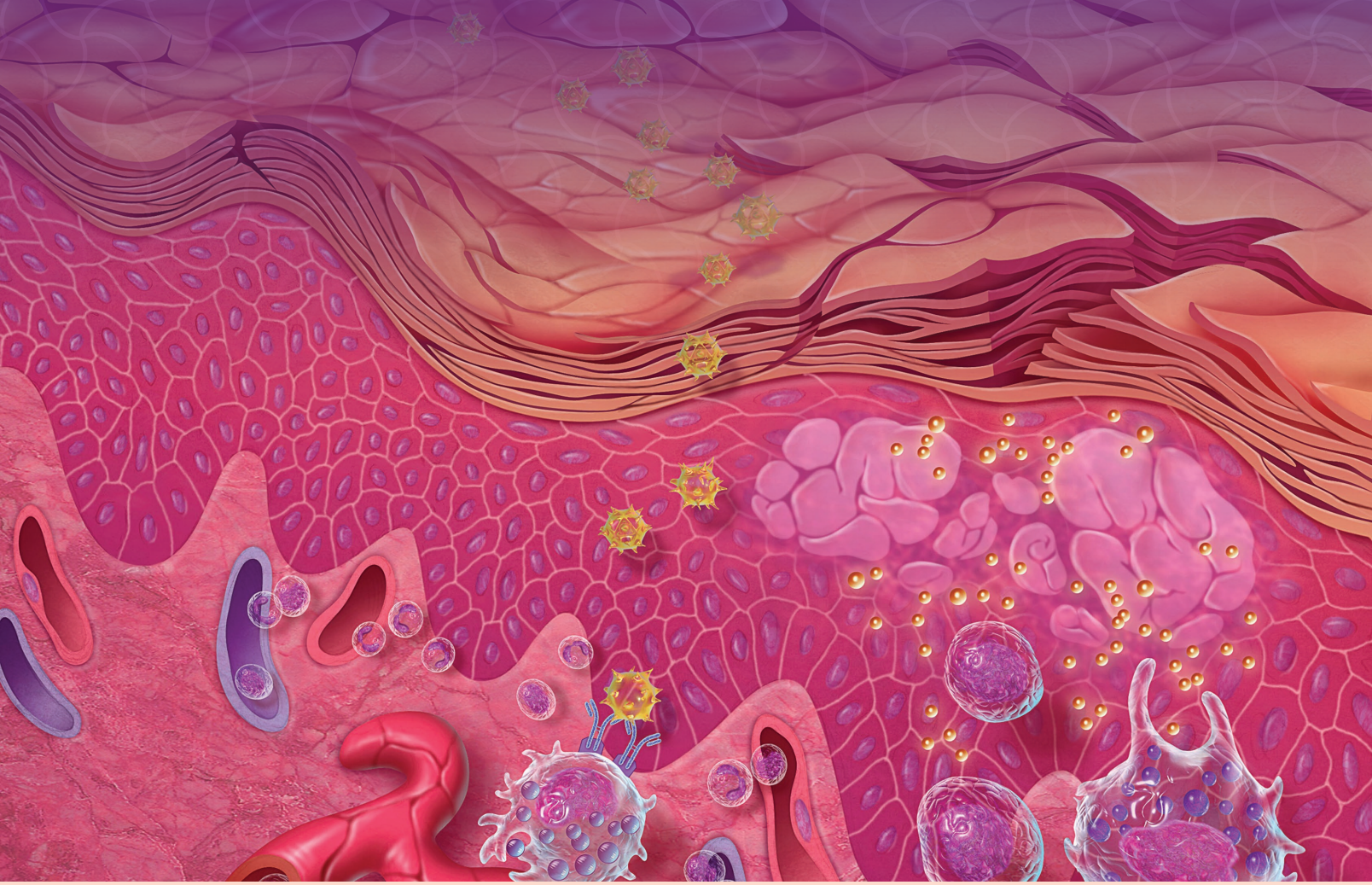
A CME/CE-CERTIFIED SUPPLEMENT TO
Dermatology News AND cutis

Atopic Dermatitis: Beneath the Surface

Individualizing Care for Patients with Moderate-to-Severe Disease



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Atopic Dermatitis: Beneath the Surface

Individualizing Care for Patients with Moderate-to-Severe Disease

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Program Overview

Atopic dermatitis (AD) can affect people of any age and can range in intensity from nonlesional to severe. Symptoms of AD have a significant negative impact on patients' overall quality of life. In recent years, basic research has revealed many aspects of the complex, multifactorial inflammatory process that underlies this burdensome disease. Discoveries involving the pathophysiology of the immune response have led, in turn, to awareness of new potential targets for AD therapies. Recently approved agents are indicated for moderate-to-severe AD; other agents now under investigation are designed to address other newly discovered mechanisms of disease.

This presentation uses 3D animation to explore what happens "beneath the surface" of AD and to graphically convey how available and emerging therapies provide a range of therapeutic options, allowing clinicians to better tailor therapy for their patients with AD of varying degrees of severity.

Target Audience

This activity has been designed to address the educational needs of dermatology specialists, including physicians, physician assistants (PAs), nurse practitioners (NPs), and nurses.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Describe the current understanding of the underlying pathophysiology of atopic dermatitis (AD)
- Assess the severity of AD
- Review mechanisms of approved and emerging agents for AD
- Discuss individualized guideline-concordant strategies for managing patients with moderate-to-severe AD

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Note to Readers

The content of this supplement is an expanded version of the CME-certified symposia presented by the author at 2 recent dermatology conferences (Coastal Dermatology Symposium, October 4, 2019, Seattle, Washington; Las Vegas Dermatology Seminar, November 9, 2019, Las Vegas, Nevada). The live presentations included video animations illustrating the pathophysiology of atopic dermatitis (AD) and the mechanisms of action of available and emerging therapeutic agents for treating AD. Readers may access those videos via the internet by clicking the links included in this document. Also included here are answers to some of the frequently asked questions posed by attendees at the symposia, along with clinical pearls offering practical advice on managing patients with AD.

Overview

Eczema is an inflammatory skin condition characterized by groups of lesions with variable degrees of exudate and scaling. Atopic dermatitis (AD) is a chronic clinical variety of eczema[1]; it affects up to 20% of children and up to 10% of adults.[1-3] The prevalence of AD decreases by about 1% after age 12 years.[4] AD has a significant burden of disease and is associated with substantial comorbidities.[5-7]

Clinical manifestations include erythema, pruritus, edema, xerosis, erosions and excoriations, oozing and crusting, and lichenification.[8,9] Studies have demonstrated that itching is the most prominent bothersome symptom reported by patients with AD.[10-12] Nearly 90% of patients with AD reportedly itch every day; 69% of these patients report that itching lasts 12 hours a day and that the itching is unbearable. Pain is associated with the itching in 50% of patients with AD. Itch substantially impairs sleep, whether by impeding falling asleep or causing frequent awakenings.[12] Nearly all patients with AD (90%) report that itching disrupts sleep at least 1 night a week, and 50% have disrupted sleep owing to itching at least 5 nights a week.[12]

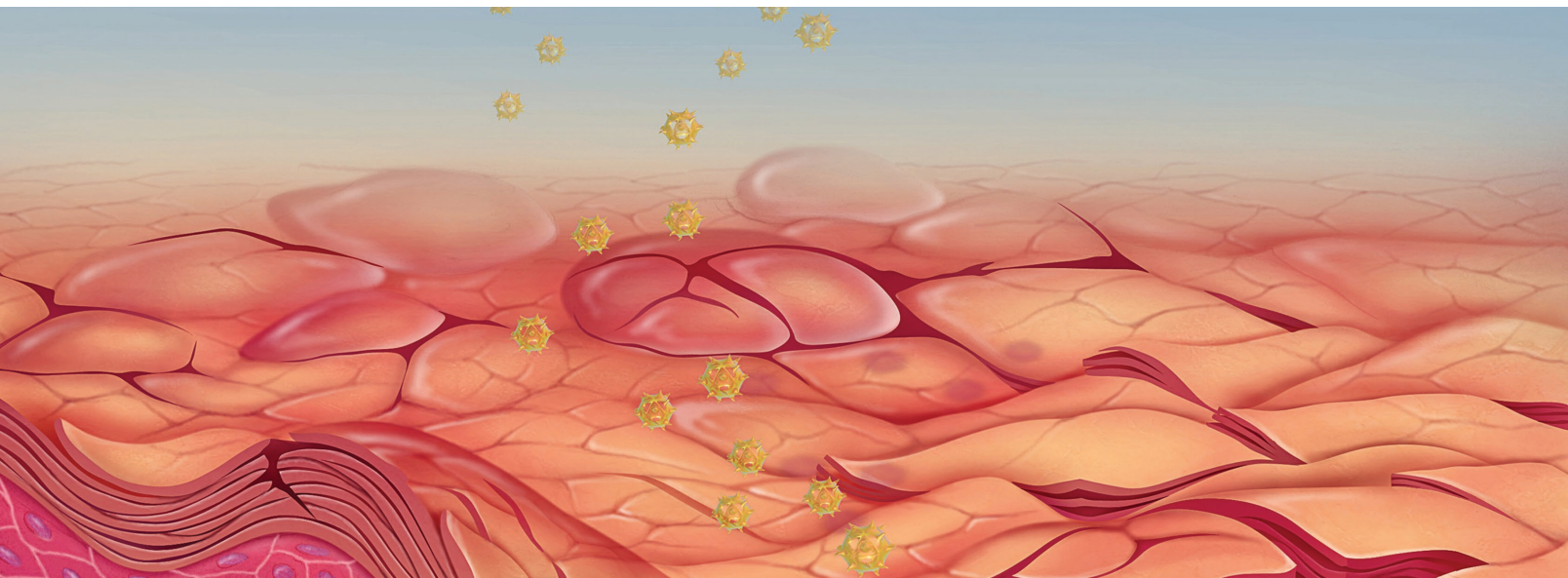
AD is a multifaceted disease that affects every aspect of a patient's life. AD is associated with other atopic comorbidities, including asthma, nasal rhinitis, and allergic conjunctivitis.[12,13] It is also linked to numerous other medical and psychiatric comorbidities, including bacterial, viral, and fungal infections and other immune-mediated disorders.[12-16] There is limited and conflicting evidence regarding a possible association with cardiovascular disease.[13,17,18] AD can interfere with productivity at work or school.[19] Put simply, AD significantly impairs quality of life.[20,21]

Most (70%) patients with AD have a family history of AD or other atopy (asthma, allergic rhinitis).[9,22-24] Patients with 1 parent who has AD have a 3-times higher risk of developing AD; the risk is 5 times greater if both parents have AD.[9,22-24] Living in an urban center or a colder climate with low humidity increases the risk for AD.[22] Data suggest females are at slightly higher risk than males for AD.[25]

The best-studied genetic trait associated with AD involves mutations in the *FLG* gene, which regulates the production of filaggrin, a filament-associated protein that binds to keratin fibers in epithelial cells.[26-31] *FLG* mutations result in dry skin, and their presence predicts severe chronic AD. However, while the presence of an *FLG* mutation increases the likelihood of having more severe AD, some patients who have this mutation do not have AD, and many other patients with AD do not have the *FLG* mutation.[32] In addition, evidence suggests that proinflammatory cytokines can affect filaggrin expression.

Other factors that have been linked with disease severity include concomitant IgE sensitization early in life; colonization with or increased susceptibility to *Staphylococcus aureus* infection; extended disease course; and environmental or food allergies.[1,2,5,6,20,33]

I explain to patients that the thickening and the leathery patches that appear on their skin is really a defense mechanism that helps protect their body from the effects of all the scratching.



Can AD Be Prevented?

Research on newborn babies examining transepidermal water loss (TEWL) found that those with higher TEWL were more likely to develop AD later in life.[34] In light of this, clinicians have aimed to decrease TEWL by moisturizing infants and avoiding alkaline soaps and other potentially drying skin cleansers.[35]

However, results of 2 recent "disruptor" studies have called this approach into question.

In the PreventADALL study, infants were randomized to a skin intervention (bathed in water with liquid paraffin and trilaureth-4-phosphate oil along with their faces treated with Ceridal cream), food intervention (introducing infants early to peanuts, milk, wheat, and eggs), a combination of the food and skin intervention, or no intervention for 1 year.[36] The investigators found that AD was more common in those infants who received either the food or the skin intervention compared with those infants who received either both or neither interventions. The authors conclude that this finding suggests that the individual interventions may have "possibly enhanced" the onset of AD.

A second investigation, the Barrier Enhancement for Eczema Prevention (BEEP) study, reported that the application of an emollient for 12 months did not prevent eczema and may have led to increased skin infections and a possible increase in IgE food allergy.[37] Together, these studies suggest that the use of moisturizers in infants has no effect on the development of AD. However, these studies used gels or creams and not heavier oil-based ointments or moisturizers, leading clinicians to question if the studies used the wrong moisturizer and if the use of heavy moisturizers might lead to different results.

Beneath the Surface: Pathophysiology of AD

Atopic dermatitis is a disease of barrier dysfunction (the "outside in" model) and inflammation (the "inside out" model), primarily driven by Th2 cell activity.[38,39]

Defects in the skin barrier enable irritants (such as bacteria, viruses, and allergens) to more easily penetrate the outer barrier and enter the epidermis. Healthy skin prevents TEWL or dehydration by keeping water and moisture in; barrier defects allow water (moisture) to be released (increasing TEWL), leading to dehydrated and drier skin (**Figure 1**). At the same time, abnormalities in the immune system result in the production of Th2 cytokines that downregulate expression of proteins of epidermal differentiation (including filaggrin) and lipids. Pathogens trigger an immune response in dendritic cells, which promote the activation of T cells. These cells, in turn, produce the cytokines that cause AD symptoms, such as interferon from Th1 cells and various interleukins (IL) from Th2 cells. The cytokines interact with structures in the skin to produce the characteristic lesions of AD and its common symptoms.

Pruritus is the hallmark symptom of AD and the symptom that most patients with AD identify as being the most burdensome (**Figure 2**).[10-12]

Figure 1. Pathophysiology of AD

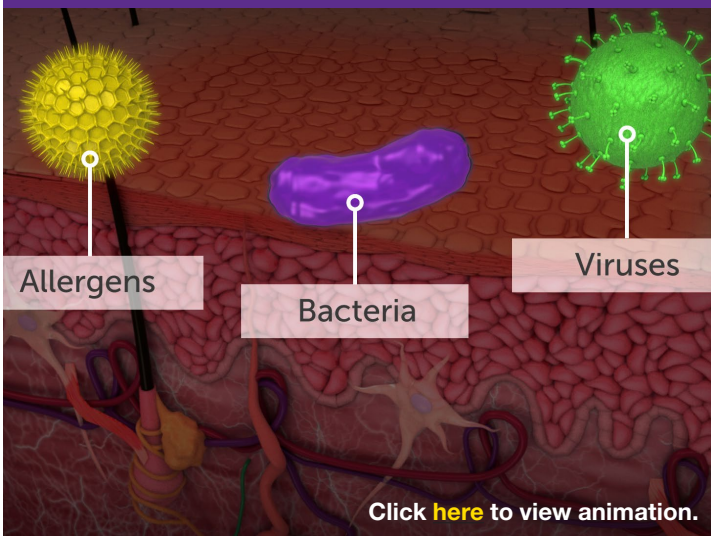
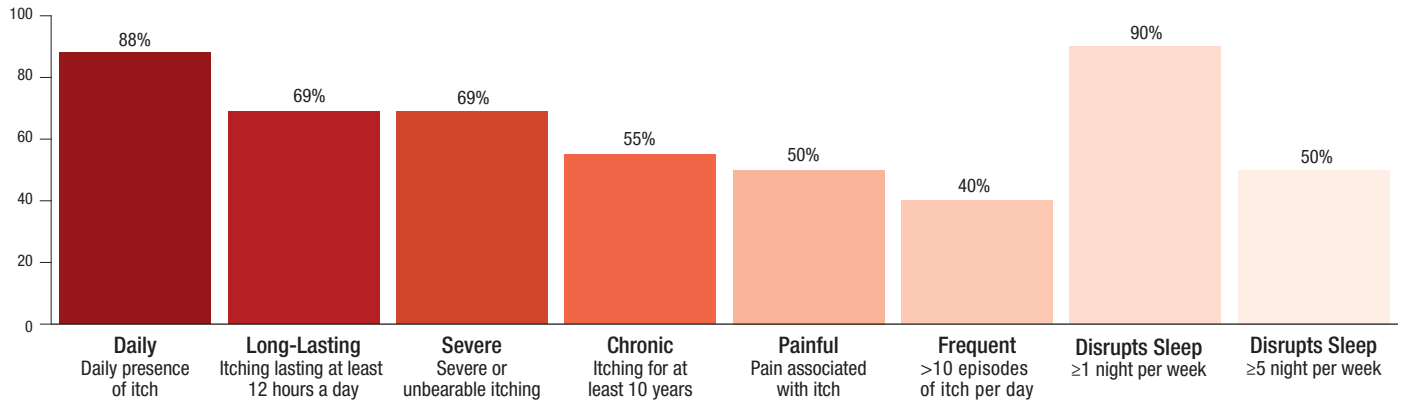


Figure 2. Persistent Itch: The Most Burdensome Symptom of AD



Sources: Dawn et al[10]; O'Neill et al[11]; Simpson et al.[12]

Pruritus is associated with defects in the skin barrier (**Figure 3**). When epidermal cells lose water, they shrink, allowing entry to pathogens, which penetrate into the deeper dermal layers. These irritants activate the immune response in dendritic cells, which then migrate to lymph nodes and stimulate T cells, which, in turn, produce higher levels of inflammatory cytokines. The cytokines most frequently associated with pruritus in AD include IL-4, -13, and -31. IL-31 is considered the "itch" cytokine and is strongly associated with chronic pruritic dermatologic disorders.[40] This immune response stimulates increased blood flow and inflammation in the outer skin layers. Increased itching promotes scratching, which further damages the skin barrier and triggers an even greater inflammatory response, marked by increased redness in the AD lesions.

It has been generally stated that AD was a disease of childhood that resolves with age. However, data from 2 longitudinal birth cohorts—the Avon Longitudinal Study of Parents and Children (ALSPAC) of 9894 children in the UK, and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study of 3652 children in the Netherlands—followed children from birth through age 11 and 16 years, respectively, and found that the life course of AD is not homogeneous.[41] In fact, these 2 studies identified 6 different subtypes or categories of AD. The most prevalent subtype was 1 in which patients were unaffected (nonlesional) or had transient disease. Among patients who were affected, the most prevalent subtype included persons who had an early onset and early resolution of AD. Individuals with an early onset were more likely to eventually develop asthma and food allergy, whereas those with a later onset were more likely to develop allergic rhinitis. The studies identified 2 subtypes of persistent disease: early-onset that persisted and early-onset that resolved later. A last subtype included individuals in whom AD developed later in childhood but resolved fairly quickly. This subgroup did not appear to have a filaggrin abnormality, but these children did have a high rate of asthma. These 2 studies were performed in different countries and had similar results, which support the validity of the findings.

Evidence suggests that there are differences in the underlying immunology of AD based on age of onset (**Table 1**). Th2 activation occurs in both age groups; however, there appears to be greater Th17-related inflammation and increased adenosine monophosphate (AMP) with AD onset during infancy/young childhood compared with onset in older children or adults.[42] The characteristic pattern of AD is also different in infants and young children, affecting the face, neck, and extensor skin surfaces; in adolescents and adults, AD lesions often involve lichenification and may be localized to the flexural fold of the extremities.[39] *FLG* mutations are common in childhood onset but rare in adult-onset AD.[43] Finally, about 1 in 3 children with early-onset AD have food allergies, which are not as common in those with adult-onset AD.

Figure 3. The Itch-Scratch Cycle

Table 1. Underlying Immunology of AD by Age at Onset

Infants/Young Children	Older Children/Adults
Th2 activation	Th2 activation
More Th17-related i nflammation, increased adenosine monophosphate (AMP)	Less Th17, less AMP involvement
Increased AMP involvement	Less AMP involvement
Characteristic pattern: face, neck, extensor skin surfaces	Skin lesions often involve lichenification, localized to flexural fold of extremities
Childhood onset: *FLG* mutations common	Later onset: *FLG* mutations rare
Food allergy in ~1/3 children with AD	

Sources: Brunner et al[42]; Schneider et al[39]; Rupnik et al.[43]

Assessing AD Severity

Diagnosis of AD is clinically based, relying on historical features, morphology, and skin lesion distribution.[44] Clinical features of the rash vary by age, race, and ethnicity. In infants and children, the rash affects extensor regions and the face; with age, the rash affects the hands, neck, and eyelids. In patients with skin of color, the eczematous lesions may be more papular, involving small raised bumps, as compared with flat plaques observed in patients with lighter skin.

Several guidelines are available to assist clinicians in diagnosing AD, including those by the American Academy of Dermatology (AAD),[1,44] the Joint Task Force Practice Parameter,[39] and the Italian Consensus Statement.[45]

The AAD guidelines identify essential, important, and associated features of a diagnosis of AD.[1,44] The two *essential* features that must be present for an AD diagnosis include pruritus and the characteristic chronic relapsing rash of eczema. In addition, *important* features that are frequently observed in patients with AD and that support a diagnosis of AD include an early age of onset; atopy or a genetic predisposition to allergy; IgE reactivity; and xerosis. Other nonspecific *associated* features that are suggestive of AD include atypical vascular responses; keratosis pilaris; pityriasis alba; hyperlinear palms; ichthyosis; involvement of skin around eyes/mouth/ears; involvement of hair follicles; lichenification; and prurigo lesions.

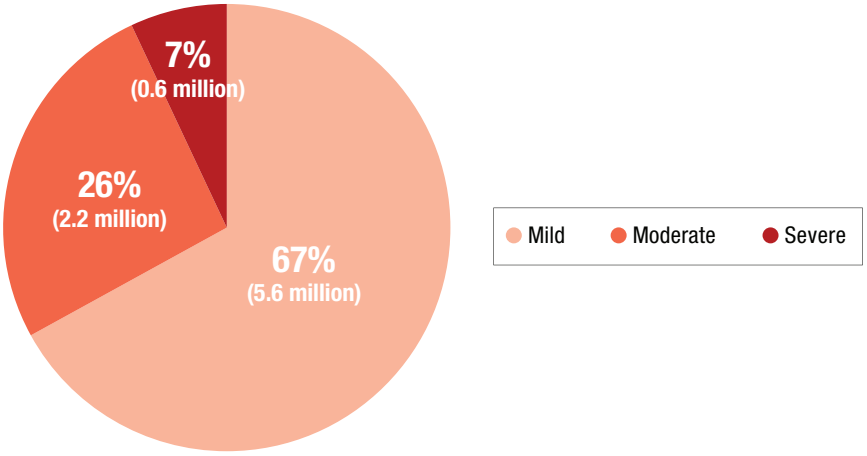
Determining disease severity is important because severity informs treatment. Mild AD is generally considered disease that affects less than 10% of the body surface area (BSA) with minimal symptoms. In general, these are patients who can be managed with topical therapy alone. Individuals are considered to have moderate-to-severe AD when they have 1 or more of the following features[8]:

- More than 10% BSA, or, regardless of BSA, individual lesions with moderate-to-severe features
- Involvement of highly visible areas or those important for function (eg, neck, face, genitals, palms, and/or soles)
- Significantly impaired quality of life.

There are a variety of clinical assessment tools or disease-severity scoring systems that clinicians may find useful in assessing AD severity.

Data from the 2007 National Survey of Children's Health, studying children from birth through age 17 years, found that about 2/3 (67%) of the patients were categorized as having mild AD, 26% had moderate AD, and 7% had severe AD (**Figure 4**).[46,47] However, this study defined severity according to signs and symptoms, extent of disease, persistence, and ease of disease control; it likely did not consider whether the disease was highly visible or in a highly sensitive area.

Figure 4. Severity of Childhood AD (0-17 years) According to the National Survey of Children's Health 2007

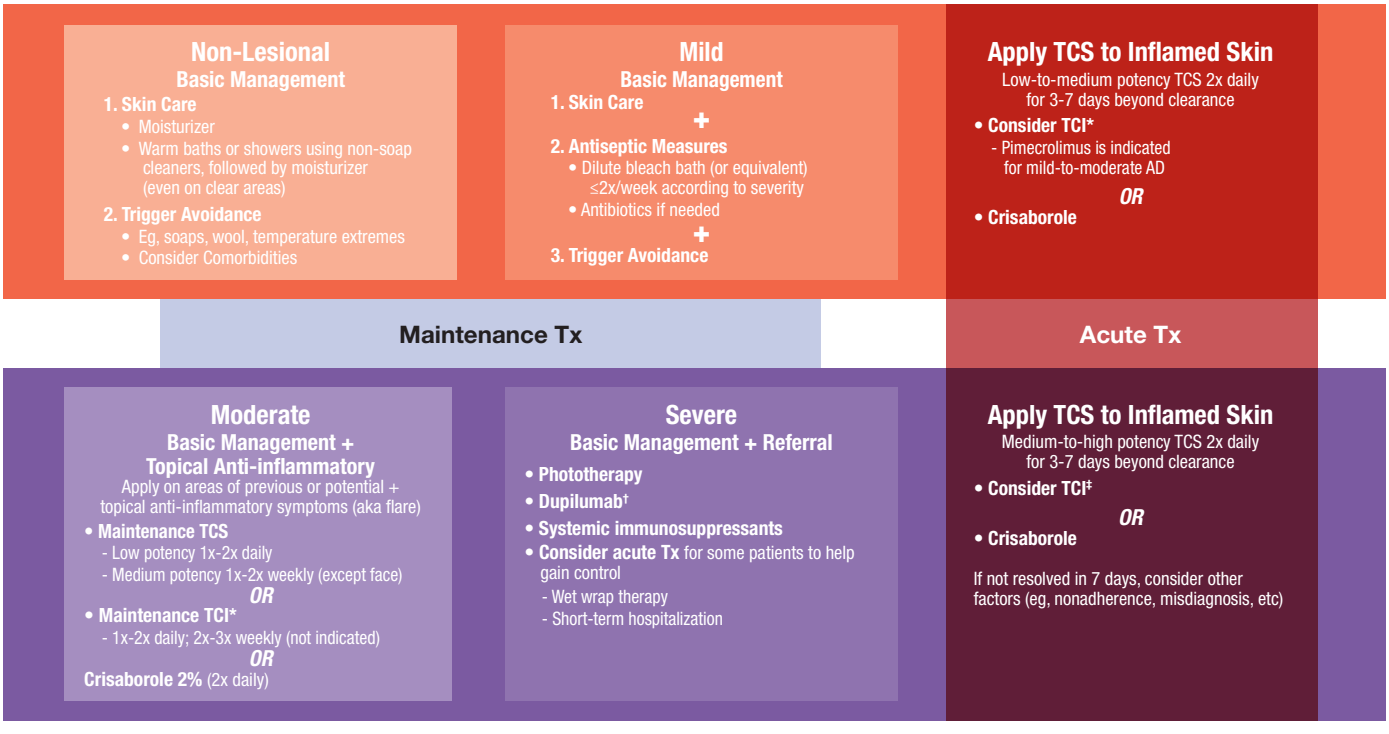


Sources: Kim et al[46]; Silverberg et al.[47]

Treating AD: How AD Drugs Target Disease Mechanisms

A growing understanding of the pathophysiology of AD has allowed investigators and clinicians to fine-tune treatments that more specifically target the origins of the disease, which has led to greater efficacy and reduced side effect profiles. In addition, therapy can now be targeted to the level of disease severity; topical therapy is not sufficient to manage severe AD (**Figure 5**).

Figure 5. Stepwise Care for AD: Matching Therapy to Severity



*Pimecrolimus is indicated for mild-to-moderate AD. †Dupilumab is indicated for patients ≥12 years with moderate-to-severe AD. ‡Tacrolimus is indicated for moderate-to-severe AD.
Source: Adapted from Boguniewicz et al.[48]

The goals of treatment are to reduce symptoms (particularly pruritus), heal the skin, and prevent exacerbations and flares.[39,44] When treating AD, it is also imperative to minimize therapeutic risks and infections because patients with AD are more susceptible to infections. The process of treatment selection is optimized when the preferences of patients (and/or caregivers) are considered.

If my patient tells me "I can't handle giving myself a shot," I will educate and encourage them, saying, "Yes, you can do a shot, and I'm going to tell you why I think this is the best course for you." This may take some time. Ultimately, I remind my patients that we are a team: "We're going to work together to get you better."

Patients with AD may not have normal skin, regardless of whether they have lesions or clear skin. It is therefore imperative to treat the entire skin in order to maintain control, which involves educating and counseling patients (and their caregiver) about general skin care—particularly the use of gentle cleansers, gentle moisturizers, and sunscreen. Although clear guidelines are lacking regarding how frequently or infrequently patients with AD should bathe, patients should always be educated regarding proper bathing and moisturizing techniques: the use of dye-free, fragrance-free emollients—creams, ointments, or oils but not lotions.[44] Following these instructions can be particularly challenging for younger patients who want to try fragrance-infused bath gels or soap from hotels.

I tell my patients to bathe every day and use a soak and seal. I recommend warm (not overly hot) water. After soaking—and before leaving the bathroom—they need to seal the moisture in by using a heavy moisturizing cream or an ointment.

What moisturizer is recommended for children with AD after bathing?

There really isn't one specific product that I recommend, although I often recommend they use a cream over an ointment because it's less sticky. However, I usually educate patients that, while lotions and thinner creams may be less sticky, they may not hydrate the skin to the same extent as thicker creams or ointments. In general, I recommend a good over-the-counter heavy cream/moisturizer from a local store, not a higher-end product from a specialty store.

The evidence supporting bleach baths is not consistent. In fact, a recent Cochrane Database systematic review of 5 studies concluded that both bleach and water baths had comparable effectiveness in reducing the severity of AD, with no differences in colonization with *S. aureus* or skin infection between the 2 types of baths and no differences in adverse effects.[49] The benefits might be in the hydrating and debriding in the bath, not the bleach that provides the benefit. Nevertheless, despite good data demonstrating benefits, this approach is an inexpensive and easy recommendation that patients can integrate into their treatment regimen. As with all baths, it should be followed by sealing in the moisture.

What should I tell my patients about taking a bleach bath?

First, I recommend cheap household bleach, using about 1/2 cup diluted into a full tub, or less bleach in less than a full tub, and tell my patients to soak to the neck but keep their head above the water. It's similar to a swimming pool so there really isn't a danger to putting their head under. I recommend my patients soak in a bleach bath about 3 times a week. When they get out of the tub, I tell them to "soak and seal," using a heavy moisturizer.

Wet wrap therapy can also be integrated into routine care, with or without bathing.[44] An easy approach is to apply a mid-potency topical steroid to the flare, wrap it with a washcloth with hot (not boiling) water, and then cover the washcloth with plastic wrap for at least 30 minutes. This process debrides and hydrates the skin, increasing the ability of the medication to penetrate. Another method is to apply wet gauze wraps over topical steroid applied to wet lesional skin, with dry gauze wraps placed on top and left on overnight.

Temperature extremes are another factor to consider in patients who sweat a lot at night; they are more likely to be scratching and flaring than those who sleep in cooler pajamas and room temperatures. Patients with asthma or allergic rhinitis may also have seasonal allergies causing flares. Coarse fabrics are another potential trigger of itch and should be avoided.

I tell my patients to shop with their fingers, not their eyes. If the product seems beautiful but it makes you itchy, don't buy it!

Treating Mild AD

Patients with mild AD have localized mild plaques that often respond to topical therapies, including low- or mid-potency steroids, nonsteroidal immunomodulators, and crisaborole.

Topical Calcineurin Inhibitors (TCIs)

Topical calcineurin inhibitors (TCIs) are available as a cream (pimecrolimus; approved by the US Food and Drug Administration [FDA] for mild-to-moderate AD) or as an ointment (tacrolimus; FDA-approved for moderate-to-severe AD). Once applied to the skin, the drug is absorbed and penetrates through to the dermal layer (**Figure 6**). Molecules of the drug enter the cell, where they bind to a protein called macrophillin-12. This complex then binds to another intracellular molecule, calcineurin. In this bound state, calcineurin is unable to penetrate the nucleus of the cell. Lower levels of calcineurin result in reduced production of cytokines, especially interleukins, interferon-gamma, and tumor necrosis factor (TNF)-alpha. TCIs exert their activity in various immune cell types, including T cells, mast cells, neutrophils, basophils, and eosinophils. One potential advantage of these agents compared to steroids is a lower risk of skin atrophy.

In fact, because these nonsteroidal agents don't cause thinning of the skin, they can be used around the eyes, on the face, or in the skinfold. However, it is important to educate patients that TCIs may cause burning and stinging.

Q&A

How can I manage the stinging and burning that is associated with crisaborole?

One strategy is to first use a topical steroid in that area for a few days until the area calms down. Crisaborole is an ointment; some people store the drug in a refrigerator, thinking that will reduce stinging and burning, although there is no evidence to support that idea. Refrigerating an ointment makes it heavy and harder to apply. It's worth noting that, for many patients, TCIs can also sting and burn when first applied.

Figure 6. TCIs: Mechanism of Action

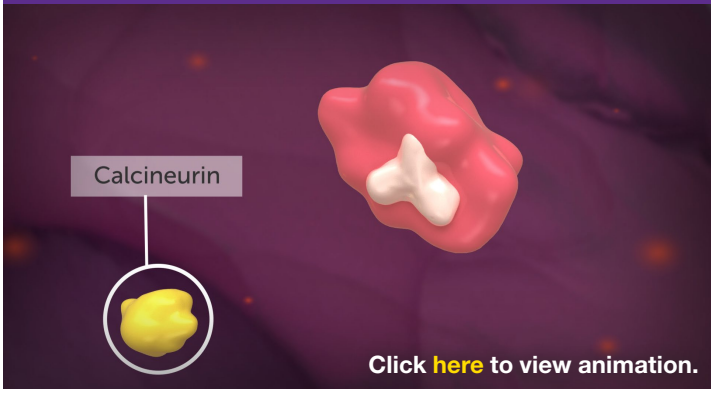


Figure 7. PDE4 Inhibitors: Mechanism of Action

PDE4 Inhibitors

Another aspect of AD pathophysiology involves proinflammatory enzyme activity within various types of immune cells. The phosphodiesterase-4 (PDE4) enzyme hydrolizes cyclic adenosine monophosphate (cAMP), producing AMP. Normally, cAMP downregulates the production of inflammatory cytokines through its actions on various signaling pathways. However, in people with AD, PDE4 becomes overactive, resulting in excess AMP levels and increased cytokine production.

Topical agents known as PDE4 inhibitors, such as crisaborole, address this aspect of the AD disease mechanism (**Figure 7**). The drug penetrates into the dermal layer, where it is absorbed by the immune cells. The drug then binds with the PDE4 enzyme and blocks its ability to degrade cAMP. With increased intracellular levels of unbound cAMP available, the downstream signaling pathways continue to be activated, thus reducing the production of inflammatory cytokines including interleukins, TNF-alpha, and interferon-gamma. The result is a reduction in the severity of AD symptoms.

Crisaborole is a topical PDE4 inhibitor approved by the FDA for treating mild-to-moderate AD in adults and children 2 years of age or older. In phase 3 trials, crisaborole demonstrated efficacy vs vehicle in bringing symptoms of AD under control, measured as a reduction in total sign score compared to baseline.[50,51] As is true with TCIs, crisaborole can be applied to the face, eyelids, skinfolds, and hands. The drug may cause some stinging or burning. For patients who are very excoriated, it may be beneficial to first administer a topical steroid for a few days prior to initiating treatment with the nonsteroidal topical agent to calm down the disease and minimize the stinging and burning.

Q&A

Does apremilast work in AD?

Apremilast is an oral PDE4 inhibitor. It was studied in AD but responses were inconsistent; it appears the pharma companies will not be pursuing an AD indication for apremilast.

clinical pearl

Patients are more likely to tolerate the stinging and burning that accompanies topical AD therapies if you counsel them that such effects do not necessarily indicate a contact allergy.

Treating Moderate-to-Severe AD

As the severity of AD increases, it is important to consider both acute management and long-term control (maintenance). If topical agents are not sufficient to gain control in patients with moderate-to-severe disease, these patients will likely require systemic therapy. A number of systemic immunosuppressants—including azathioprine, cyclosporine A, methotrexate, and mycophenolate mofetil—have been used off-label to provide nontargeted, broad immunosuppression to calm the disease.[52] However, none of these agents have been approved by the FDA for the treatment of moderate-to-severe AD. (Cyclosporine is approved in Europe for AD.) Systemic corticosteroids can be used, although the AAD recommends avoiding the use of systemic corticosteroids whenever possible.

As of December 2019, the only biologic agent available for managing moderate-to-severe AD is dupilumab. Dupilumab, a human monoclonal IgG4 antibody administered as a subcutaneous injection, is FDA-approved for adults and, as of 2019, adolescents age 12 years and older.

As noted above, in patients with AD, skin barrier defects permit antigens to enter and penetrate through the dermal layers. These antigens are recognized by immune cells, including T2 cells, triggering the release of a cascade of inflammatory mediators, among the most important of which are interleukins 4, -13, and -31. On T cells, the Type 1 receptor binds only with interleukin-4; the Type 2 receptor binds with interleukin-13 as well as interleukin-4. This binding activity amplifies intracellular signaling, leading to increased production of cytokines and promoting AD symptoms, including inflammation and pruritus. This action, in turn, affects 3 of the main disease mechanisms of AD: decreases in skin barrier function, a class switch to IgE, and Th2 differentiation.[53]

Dupilumab blocks the IL-4/IL-13 pathway **(Figure 8)**. The agent binds specifically to the IL-4R-alpha subunit of the receptor, which inhibits interleukin-4 signaling via Type 1 receptors and both interleukin-4 and -13 signaling through Type 2 receptors. Blocking these cell signals results in lower production of proinflammatory mediators, including cytokines, chemokines, and IgE.

The safety and efficacy of dupilumab were established in placebo-controlled trials involving more than 2100 adults with AD. The patients in these trials had more than 50% body surface area affected by AD, and most had had AD for the majority of their lives. Co-primary endpoints included the percentage of patients achieving Investigator's Global Assessment (IGA) of 0/1 and 2-point or higher improvement from baseline, and Eczema Area and Severity Index of at least 75% (EASI-75) improvement from baseline.[54] At the end of 52 weeks, about 36% of patients receiving dupilumab were "clear" or "almost clear" compared with 13% of patients receiving placebo, and about 65% of the patients receiving dupilumab (versus 22% of the patients receiving placebo) had at least 75% improvement.[55-57] Dupilumab demonstrated significant clinical benefits across a number of AD severity measures, including the EASI-75, IGA, and SCORAD, as well as a significant decrease in pruritus.[55-58] Dupilumab may be used with or without topical corticosteroids (TCS). Data indicate that adding dupilumab to TCS is more effective than TCS alone.[54,59,60]

An important finding is that dupilumab appears to rapidly improve pruritus, even before rash improves.[61] Pooled analysis data from 2 16-week phase 3 randomized clinical trials in adults with AD (N=1379) examined the effect of dupilumab monotherapy, either 300 mg every week or every other week, on the visual analog (1-10) peak pruritus numerical rating scale (NRS). Clinically significant improvement in itch was reported as early as day 3 to 4 after treatment initiation, and at 16 weeks, significantly more patients who were treated with dupilumab (38.4% with dupilumab 300 mg once every 2 weeks and 39.6% dupilumab 300 mg once every week) reported ≥4-point reductions in NRS versus placebo (10.9%; $P<0.0001$).[61]

Data from the phase 3 clinical trial leading to FDA approval for use in adolescents reported biweekly administration of dupilumab resulted in 24% of patients getting to clear or almost clear after 16 weeks, and about 41.5% of adolescent patients had a 75% improvement in the EASI score at the end of 4 months.[62]

Figure 8. Dupilumab: Mechanism of Action

clinical pearl

Topical medication for AD should always be applied before applying moisturizers.

Q&A

How do you use topical steroids after lesions have cleared?

I treat until clear if possible. Afterwards, I recommend that the patient use a topical corticosteroid twice a week or every other day—on an indefinite basis—to prevent flares, along with regular nonmedication maintenance therapy (moisturizers and bathing). Alternatively, topical nonsteroidal agents (TCIs or PDE4 Inhibitors) may be used as "proactive" therapy to minimize signs and symptoms as well as flares.

Initial clinical trial durations were 16 weeks; a long-term safety study in adults lasted 52 weeks.[54] Because dupilumab acts as an immunomodulator, not an immunosuppressant, it poses a reduced risk of serious infections vs placebo (**Table 2a**). There is a slightly higher risk of the more benign herpes infections. There is, however, an increased risk of conjunctivitis (which generally resolves on therapy), affecting about 11.5 patients per 100 patient years (**Table 2b**).[63-65] This risk appears to increase with increasing disease severity, and a prior history of conjunctivitis, and decreases with a good response to dupilumab.[63,65] In a pooled analysis, 13.2% of the patients receiving dupilumab experienced injection site reactions, compared with 6.5% of the patients on placebo.[66] Although dupilumab is a biologic, it is not necessary to check for tuberculosis prior to initiating therapy as it targets the IL-4 and IL-13 cytokines, which have not been found to host defense mechanisms against tuberculosis or most other infectious agents.[64] Further, there is no requirement for routine laboratory monitoring, although a baseline panel may be helpful.[64,67]

Table 2a. Safety Concerns, Dupilumab vs Placebo: Risk of Infection				
	Patients/100 person-years			
Infection type	Placebo	Dupilumab 300 mg q2w	RR (95% CI)	*P*=
Infections leading to treatment discontinuation	**0.99**	**0.34**	0.35 (0.04, 2.95)	0.33
Serious/severe infections	**3.98**	**2.39**	0.60 (0.25, 1.42)	0.25
Skin structures and soft-tissue infections	**11.26**	**5.87**	0.52 (0.30, 0.90)	0.02
Non-herpetic skin infections	**26.56**	**15.67**	0.59 (0.42, 0.83)	0.003
Adjudicated skin infections: Dupilumab monotherapy	**31.15**	**19.40**	0.62 (0.40, 0.97)	0.04
Adjudicated skin infections: Dupilumab + topical steroid	**23.53**	**11.10**	0.40 (0.26, 0.84)	0.01

Sources: Eichenfield et al.[64]; Fleming et al.[68]

Table 2b. Safety Concerns, Dupilumab vs Placebo: Incidence of Conjunctivitis			
Placebo (n=1091)		Dupilumab 300 q2w (n=746)	
# Pts	Pts/100 person-years	# Pts	Pts/100 person-years
10	1.975	33	11.445

Sources: Akinlade et al[63]; Eichenfield et al[64]; Treister et al.[65]

Q&A

How long should a patient stay on dupilumab?
AD is a long-term problem. Once I initiate dupilumab therapy in patients—including adolescents—I usually leave them on it for as long as possible, as long as it remains covered by insurance and as long as they tolerate the treatment.

How should I manage the rash that occurs in some patients taking dupilumab?
There are reports of patients developing a red, scaly rash on the face, although I have not seen any such cases in my practice. There are case reports of this being treated successfully with itraconazole.

Emerging Therapies

Many agents for the management of AD are undergoing clinical trials, offering different mechanisms of action targeting various aspects of disease pathophysiology (**Table 3**). Space does not permit a discussion of all of these mechanisms.

Table 3. Emerging Agents for AD		
Agent	Target	Route of Administration
Abrocitinib	JAK1	Oral
Baricitinib	JAK1/2	Oral
Delgocitinib	Pan-JAK (1/2/3/Tyk2)	Topical cream
Ligelizumab	IgE	Subcutaneous injection
Ruxolitinib	JAK1/2	Topical cream
Tapinarof	AhR agonist	Topical cream
Tradipitant	NK1 receptor	Oral
Tralokinumab	Il-13	Subcutaneous injection
Upadacitinib	JAK1	Oral
Ustekinumab	Il-12/23p40	Subcutaneous injection

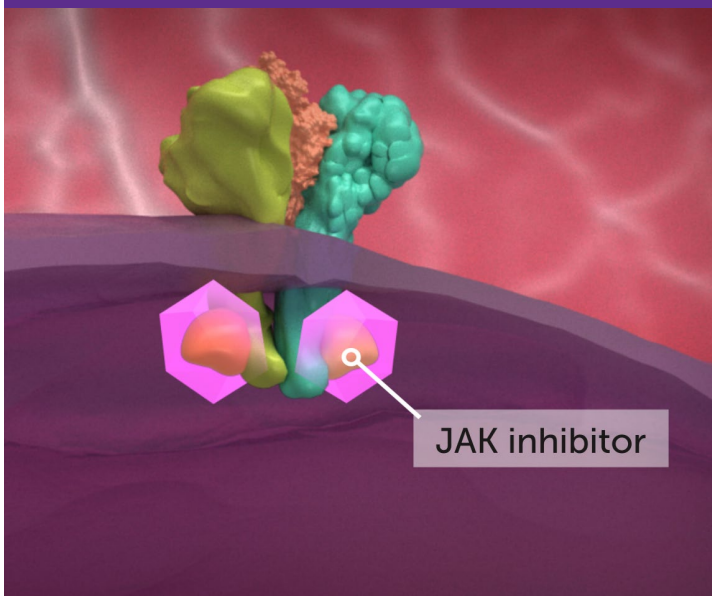
Phase 3 data are available for several Janus kinase (JAK) inhibitors, which are administered either orally or topically. The JAK family includes 4 proteins (**Figure 9**). These proteins work together in specific combinations of 2 or 3 to transmit signals from cell surface receptors, thereby activating different downstream cytokine pathways within the cell nucleus.

The process begins when a cytokine binds to Type 1 and Type 2 extracellular surface receptors.[69,70] Adenosine triphosphate (ATP) travels to the site and activates the JAKs through phosphorylation. Other proteins known as STATs migrate to and bind at the intracellular receptor, where they are phosphorylated by the activated JAKs. The STATs then translocate to the cell nucleus, where they regulate gene transcription and cytokine production.

JAK inhibitors block this process. Molecules of the drug pass through the cell membrane and selectively bind with 1 or more JAKs at the intracellular receptor level. This prevents phosphorylation and prevents STATs from becoming activated and carrying signals to the nucleus.

Different JAK combinations regulate different cytokine pathways. For example, the JAK1/JAK3 dimer mediates signals for various interleukins. The JAK1/JAK2 dimer mediates interferon gamma function, and so on. Likewise, different JAK inhibitors now in development selectively block various JAK combinations.[69,70]

Figure 9. Janus Kinase Inhibitors: Mechanism of Action



Conclusion

AD is a 2-pronged disease. Externally, defects in the skin barrier cause a loss of protection against external irritants and subsequent loss of hydration. Internally, immune dysregulation primarily involving Th2 leads to increased production of inflammatory proteins, which produce the characteristic symptoms of AD, including pruritis and erythema. Achieving optimal outcomes with AD therapy depends on an accurate assessment of disease severity and requires a holistic approach that involves appropriate bathing, skin care, and individualized treatment targeted to the severity of disease. Acute treatment focuses on gaining control of the disease, which needs to be followed by maintenance therapy to prevent recurrences and flares. Systemic therapy should be considered sooner rather than later for patients with moderate-to-severe AD. The study and FDA-approval of new topical (eg, crisaborole) and systemic agents (eg, dupilumab) and the current extensive ongoing clinical trials make the future of our patients with AD bright with the possibility of achieving improved disease control.

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