# New Insights and Treatments in Atopic Dermatitis

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**KEYWORDS**

• Atopic dermatitis • Topical and systemic treatments • Small molecule inhibitors
• Biologics • Atopic dermatitis phenotypes

**KEY POINTS**

- Atopic dermatitis (AD) is complex chronic inflammatory skin disorder.
- There is now an increased understanding of the pathogenesis of AD, resulting in discovery of much wanted new targeted therapies.
- Various AD phenotypes and endotypes are described, enabling targeted therapies in the future.
- Whether a long-term cure or sustained benefits will occur remains to be seen.

## INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin disease, with significant morbidity. The disease affects 20% to 30% of children and 7% to 10% of adults.[1] It is characterized by chronic itching, dry skin, eczematous lesions, and relapsing course. Pruritus is the sine quo non feature, causing a significant disruption of daily life. In many patients with moderate to severe AD, a chronic itch-scratch cycle causes significant morbidities such as sleep loss, impaired quality of life, and psychosocial problems, besides complications including skin infections.[2] The frequent need for treatment creates significant financial and mental burdens on families.[3] AD is also the first evidence of atopic disease in early childhood, with likely development of the atopic march of allergic rhinitis, asthma, and food allergies in these patients causing further morbidities.[2] Recent studies also link AD to other nonallergic conditions, including a risk for systemic and multiorgan infections,[4] cardiovascular diseases (coronary artery disease),[5] and neuropsychiatric disorders such as depression, anxiety, and attention-deficit/hyperactivity disorders.[5]

The treatment of AD has evolved slowly from using topical emollients in the early 1930s to topical steroids (1960s) and calcineurin inhibitors (2000s), and now, after a

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Pediatr Clin N Am 66 (2019) 1021–1033
https://doi.org/10.1016/j.pcl.2019.06.008
pediatric.theclinics.com

long wait, new biologic agents are available (2016), such as anti–interleukin (IL) 4/IL-13 antibodies. Some of the newer therapies are discussed in this article.

## PATHOPHYSIOLOGY

AD is a complex skin inflammatory disorder with multifactorial cause, including a complex interaction of epidermal barrier defects, immune dysregulation of both adaptive and innate immunity, and environmental.[6,7] There is ongoing debate triggers whether AD is a consequence of genetic mutations affecting the epidermal barrier (outside-in model) or is caused by inflammation inhibiting epidermal differentiation (inside-out model).[6] Importantly, immune activation is not only seen in AD skin but also in clinically normal-appearing skin, as well with AD-specific inflammatory changes in blood components suggesting the systemic aspect of this disease.[7,8] AD is understood to be primarily a T cell–driven disease; with a dominant T helper (TH) type 2 immune response with increased levels of IL-4, IL-13, IL-31, and chemokine ligand 18 (CCL18) cytokines and additional activation of TH22,TH17/IL-23, and TH1 cytokine pathways.[8] The lesional levels of these cytokines were shown to be significantly increased compared with healthy skin.[7,8] The IL-4 and IL-13 cytokines are produced by TH2 cells and play a key role in the pathogenesis of AD and also overproduction of immunoglobulin (Ig) E.[8–10] Filagrin (FLG), loricrin, and involucrin are downregulated in both lesional and nonlesional skin by IL-4 and IL-13, contributing to a defective skin barrier and thereby penetration of allergens and bacteria, leading to allergen sensitization and infections, which is a hallmark of AD.[7,9] IL-4 and IL-13 also inhibit production of antimicrobial peptides predisposing to *Staphylococcus aureus* infections, further enhancing skin inflammation and barrier defects.[10,11] The IL-4/IL-13–driven inflammation can also downregulate the TH1 (interferon gamma) and TH-17 (IL-17)–dependent skin defense mechanism.[8,12] Although IL-17 is increased AD lesions, its antimicrobial effects are inhibited in the presence of IL-4/1L-13.[12] TH-17 also contributes to immune dysregulation as well as barrier abnormalities by downregulating FLG cellular adhesion molecules.[12] In chronic AD, TH2 and TH22 responses are also increased with parallel activation of the TH1 axis.[8] IL-22 is identified as the key mediator for epidermal hyperplasia, whereas the IL-31 cytokine is associated with itch and correlates with disease severity.[8] The chronic inflammation in the skin with various triggers and accentuated by defects in the skin barrier results in relapsing clinical rash and itching.

## CLINICAL FEATURES

Different phenotypes of AD are now described based on IgE levels (intrinsic and extrinsic), age (pediatric and adult AD), FLG gene mutation, race, or ethnicity (Asian and European/American). Extrinsic AD is characterized by increase in total IgE (both total and allergen specific), high eosinophil count, and family history of atopic disease, whereas intrinsic AD shows normal IgE levels and lack of atopic history in the patient or in the patient's family.[13] Both show strong TH2 activation; however, in intrinsic AD there is stronger activation of TH17 and TH22 axis.[13] Pediatric AD has early onset, extensor surface involvement, a different skin microbiome,[14] and much higher levels of activated cytokines in nonlesional skin in children.[15] Ethnic differences are also seen, with Asian AD showing more parakeratosis, significantly increased TH17 axis, and cytokine profile suggesting a blend of AD and psoriasis.[16] In adult AD, FLG deficiency is common and also the peripheral blood shows TH22 polarization, unlike in child AD with TH2 dominance.[14] FLG gene mutation has been associated with a more severe and persistent form of AD but is seen in only 30% of European patients and is rare in African Americans.[17] Patients with FLG gene mutation have also been

shown to outgrow their disease with age, suggesting the complexity of AD.[17] Recognizing different endotypes/phenotypes of AD will be important to customize therapies as new targeted agents are discovered in the future.

## MANAGEMENT

The goal of treatment in AD is to reduce symptoms, prevent exacerbations, treat superinfection, minimize treatment risks, and restore the integrity of the skin. In most patients with mild disease, treatment goals are achieved with topical therapies alone, unlike in patients with moderate to severe disease, whose management is challenging.

The general principles of therapy include education and active participation of patients and their families, improving hydration and skin barrier function, eliminating exacerbating factors, and treatment of skin inflammation. At present a guideline-based or stepped-care approach for treating AD is lacking. Thus, in clinical practice, there are distinct approaches to management, and varied advice and recommendations are given to patients by both primary care providers and specialists. This

**Table 1**
**Management of Atopic dermatitis-Basic and Step-up treatments**

| Basic Management | Step-up Treatment |
|---|---|
| 1. Skin hydration<br>a. Bathing: warm baths or showers with nonsoap cleansers<br>b. Moisturizers: prompt, frequent, and liberal use of preservative-free and fragrance-free moisturizers<br>2. Allergen avoidance<br>a. Food is not common, as often considered<br>b. Need to confirm with oral challenge<br>c. Extensive testing and food elimination not recommended<br>d. Additives rare cause<br>e. Environment: dust mites, aeroallergen<br>3. Elimination of triggers<br>a. Known irritants<br>b. harsh fabrics-wool<br>c. Irritants: soap/cleansers, fragrance<br>d. Extreme temperatures<br>e. Pollutants<br>4. WWT and alternative clothing<br>a. WWT acutely and for maintenance<br>b. Derma Silk, silk Skinnies | 1. Mild-moderate AD<br>Basic management plus:<br>a. Topical antiinflammatory therapies<br>a. Acute and/or maintenance treatments<br>i. Topical corticosteroids<br>- Active: acute flare<br>Appropriate potency for 3–4 weeks with stepdown to lower potency for additional few weeks until improved<br>Proactive: in AD flare areas 2–3 times a week for months<br>ii. Topical calcineurin inhibitors<br>Recommended for >2 y of age, steroid sparing<br>Useful for Facial AD<br>iii. Newer agents: crisaborole<br>b. Adjuvants<br>a. Antihistamines: oral<br>b. Weigh pros/cons of use<br>c. Infections: bacterial, viral, fungal<br>a. Antiseptic measures: dilute bleach baths<br>b. Specific infections: antibiotics or antivirals<br>2. Moderate-severe AD<br>All of the above plus:<br>1. Newer agents: biologics<br>2. Systemic immunomodulating agents<br>3. Phototherapy<br>4. Allergen immunotherapy<br>5. Anti-IgE therapy<br>6. Hospitalization |

*Abbreviation:* WWT, wet wrap therapy.

variation causes confusion and angst for patient and families while dealing with a chronic and frustrating condition.

Good clinical management should include 2 elements: (1) basic management, and (2) step-up treatment of severe AD. Some salient features are listed in **Table 1** and **Box 1**. This article focuses on newer therapeutics, but the importance of good basic management cannot be overlooked for successful outcomes for treatment of AD. Readers are recommended to read guidance documents about patient evaluation, treatment algorithms published by the American Academy of Dermatology as well as the American Academy of Allergy, Asthma, and Immunology.[18–21]

**Box 1**
**Bathing instructions for patients with atopic dermatitis**[19]

1. Bathing is suggested for both treatment and maintenance
2. No standard for frequency and duration is established
3. Regular once-daily bathing with warm (not hot) water of short duration (5–10 minutes)
4. Limited use of nonsoap cleansers that are neural to low pH, hypoallergenic, and fragrance free
5. Generous and frequent application of moisturizers, with first soon after bathing, to improve skin hydration
6. Soak and seal: soak skin in warm water for 15 minutes, light pat dry, and seal in moisturizer for severe AD

## *Step-up Treatments*

Severe AD is a frustrating disease with a chronic and relapsing course with complications. Step-up therapies should only be considered in patients who are adherent and unimproved with vigorous, topical antiinflammatory therapies without underlying infections and in whom an alternate diagnosis is excluded. Until recently the treatment options were limited to phototherapy, systemic immunomodulatory agents, or immunotherapy, which are not evidence based and are limited because of side effects. The US Food and Drug Administration (FDA) recently approved a new biologic agent for treatment of chronic AD in adults. Many new targeted therapeutics, including small molecule agents and anticytokine proteins, are being investigated for treatment of AD, as listed in **Table 2**.

### *Small molecule agents*

Crisaborole is low-molecular-weight boron-based compound (benzoxaborole) with effective penetration in human skin. It is a phosphodiesterase 4 (PDE4) inhibitor with topical antiinflammatory activity in skin. PDE4 activity is increased in AD skin, resulting in decreased intracellular levels of cyclic adenosine monophosphate, which results in increased production of proinflammatory cytokines.[22] Crisaborole has been shown to decrease PDE4 levels and inflammation in animal models. It is rapidly and substantially metabolized to inactive molecules, thus limiting the systemic effects. The clinical efficacy and safety of crisaborole 2% ointment were established in 2 large, randomized controlled, phase 3 clinical trials in the United States involving a total of 1522 subjects ($\geq$2 years old) with mild (Investigator's Static Global Assessment score [ISGA] score 2) to moderate (ISGA score 3) AD at baseline. Most subjects (87%) were children and adolescents (2–17 years old), with approximately (33%) 2 to 6 years old. The primary efficacy variable was an ISGA score of clear or almost clear skin or an

**Table 2**
**New investigational agents for treatment of moderate to severe atopic dermatitis[25]**

| Target | Compound | Trial Phase, Clinicaltrials.gov Identifier |
|---|---|---|
| Topical Agents | | |
| AhR | Tapinarof/Benvitimod | 2a, NCT02466152/NCT02564055 |
| PDE4 | Roflumilast | 2a |
| JAK1, JAK3 | Tofacitinib | 2a, stopped |
| JAK1, JAK3 | LEO 124249/JTE-052 | 2a |
| *S aureus* | *Roseomonas mucosa* bacteria | 1/2 antecubital AD |
| *S aureus* | Coagulase-negative *Staphylococcus* | 1/2 ventral arm AD |
| PDE4 | Crisaborole | Clinical use |
| Biologics | | |
| IL-4 | Pitrakinra | 2a |
| IL-5 | Mepolizumab | 2a |
| IL-12/23P40 | Ustekinumab | 2a, NCT01806662 |
| IL-13 | Tralokinumab | 2 completed, NCT02347176 |
| IL-13 | Lebrikizumab | 2 completed, NCT02340234 |
| IL-4/1L-13R | Dupilumab | Approved for clinical use 2017 |
| IL-17 | Secukinumab | 2, NCT02594098 |
| IL-22 | Fezakinumab (IV) | 2, NCT01941537 |
| IL-31R | Nemolizumab | 2 complete, NCT01986933 |
| IL-31 | BMS-981164 | 1, NCT01614756 |
| TSLP | Tezepelumab | 1 complete, NCT00757042 |
| TSLP-R | MK-8226 | 1, NCT01732510 |
| IgE | QGE031/ligelizumab | 2 complete, NCT01552629 |

*Abbreviations:* AhR, aryl hydrocarbon receptor; IV, intravenous; JAK, Janus kinase; PDE, phosphodiesterase; TSLP, thymic stromal lymphopoietin; TSLP-R, thymic stromal lymphopoietin receptor.

improvement grade of at least 2 from baseline at the end of the 28-day period of twice-daily application of crisaborole.[23] In the 2 trials, crisaborole 2% ointment ameliorated disease severity as soon as day 8 of treatment, and produced rapid and sustained lessening of pruritus, which is an important morbidity for patients with AD. These outcomes were significant despite a strong vehicle effect relating to the benefits of emollient treatment and placebo response rates. A side effect directly implicated was application site pain (burning, stinging), occurred in at least 1% of patients.[23,24]

Crisaborole 2%, a topical nonsteroidal ointment, was approved by the FDA in 2016 for treatment of mild to moderate AD in patients aged at least 2 years. The improved risk-benefit profile makes it suitable for steroid-phobic patients and as a steroid-sparing agent. It can be used as first line of treatment or for long durations of maintenance therapy in place of topical steroids, and thus avoiding steroid side effects.

### *Biologic agents*

Various anticytokine agents are being aggressively investigated for treatment of AD.[25] One agent was recently approved for clinical use.

**Interleukin-4/interleukin-13 blockade** Dupilumab is a fully human monoclonal antibody (mAb) targeting the common alpha chain of IL-4 and IL-13 receptor, thus

blocking signaling through these cytokines. In a landmark study of phase 1, 2, and 3 trials, dupilumab treatment was shown to decrease skin inflammation and improved epidermal-associated measures with a significant clinical improvement of AD as well as associated symptoms including pruritus, anxiety, and depression.[25,26] A 52-week efficacy and safety study of dupilumab added to a medium dose of topical steroids in adults also showed similar clinical benefits compared with placebo, as observed during the earlier trial of 16 weeks.[26–28] Headache, nasopharyngitis, injection site reactions, and conjunctivitis in particular were frequently reported symptoms during the trials. Hypersensitivity reactions, including urticaria and serum sickness–like reactions, were reported in 15 subjects in the trials.[27] At present, dupilumab is the only biologic drug approved by the FDA for systemic treatment of AD. It will be interesting to know its treatment effects for allergic asthma, allergic rhinitis, or eosinophil esophagitis caused by its effects on TH2 cytokines. The phase 3 Liberty Asthma Quest trial, a large controlled study, is evaluating dupilumab efficacy and safety in adult patients with uncontrolled, moderate to severe asthma with pending results.[29] These study results will enhance the rationale of using biologics for treatment of AD and coexisting allergic disease such as asthma.

Dupilumab received FDA approval in March 2017 for adult patients (>18 years old) with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It can be used with or without topical corticosteroids. Dupilumab is available as 300-mg/2-mL prefilled injection to be self-administered as a subcutaneous injection. Initial dose is 600 mg subcutaneously followed by 300 mg given subcutaneously every 2 weeks. Injections can be self-administered at home, patients need not have autoinjectable epinephrine, and routine blood tests and laboratory monitoring are not currently required.[30] Current limitations for clinical use of dupilumab include age cutoff, cost, and insurance coverage. It is likely to be a safe and effective alternative to phototherapy or systemic immunosuppressant drugs in adults with unimproved moderate to severe AD with topical therapies. The postmarketing experience will help educate clinicians about its long-term safety, efficacy, and also dosing recommendations, and duration of treatment.

### Other T-helper 2 cytokine blockade studies

**Interleukin-13 blockade** IL-13 is a key cytokine involved in the pathophysiology of several atopic diseases.[8] IL-13–mediated signaling is initiated by binding to IL-13Ra1, which then recruits IL-4Ra to form a heterodimeric receptor complex. IL-13 also binds to IL-13Ra2, thought to function as a decoy receptor. IL-13–neutralizing antibodies interfere with IL-13 binding to IL-13Ra1, IL-4Ra, and/or IL-13Ra2. Tralokinumab is a human recombinant IgG4 mAb that binds to IL-13 and blocks interaction with IL-13 receptors. Phase II trials with the anti–IL-13 antibodies tralokinumab and lebrikizumab have shown some clinical efficacy compared with placebo. A phase 2b, randomized, double-blinded, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of 3 doses of tralokinumab administered by subcutaneous injection in adults with moderate to severe AD every 2 weeks for 12 weeks was completed, with pending results (NCT02347176, clinicaltrials.gov).[31,32]

**Interleukin-5 blockade** Blood eosinophil levels have been shown to increase in AD. IL-5 is a Th2 cytokine that is important for eosinophil recruitment. An mAb to human IL-5, mepolizumab, failed to show efficacy in patients with moderate to severe AD. In a randomized, placebo-controlled, parallel-group study of 18 patients treated with 2 single doses of mepolizumab (750 mg given 1 week apart) versus 22 patients

treated with placebo, peripheral blood eosinophil levels were significantly reduced in the treatment group compared with placebo ($P<.05$). Clinical success was not achieved, as assessed by Physician's Global Assessment, SCORAD, pruritus scoring, or thymus and activation-regulated chemokine values in the mepolizumab-treated group compared with placebo.[33]

**Interleukin-31 blockade** IL-31 is a key pruritus-inducing cytokine that is upregulated in AD. The source of IL-31 in AD lesions has been debated; IL-31–positive cells were observed either as mononuclear infiltrating cells or as cluster of differentiation 11b (CD11b)–coexpressing cells with IL-31 receptor A detected in keratinocytes and nerve fibers in the dermis of AD and in the neurons of normal dorsal root ganglia.[34] Nemolizumab (CIM331) is a humanized anti–IL-31 receptor A mAb, binds to IL-31 receptor A, and inhibits IL-31 signaling.[35] It was shown to decrease pruritus and dermatitis, and to improve sleep and clinical scores in adult patients with moderate to severe AD compared with placebo in 12-week, phase II trial (part A, NCT01986933, clinicaltrials.gov). A 52-week, double-blind extension study (part B) to assess the long-term efficacy and safety of nemolizumab when injected subcutaneously every 4 weeks or every 8 weeks was completed recently. Nemolizumab when used for up to 64 weeks was shown to be efficacious and overall well tolerated in patients with moderate to severe AD.[36] Pruritus is the most frustrating symptom of AD, causing morbidities and also being difficult to control. It is hoped that this new therapy will improve this morbidity.

**Other cytokines: T-helper 17, T-helper 22 pathways, interleukin-12, and interleukinIL-23** AD is primarily a TH2 activation disease but activation of other T-helper cells is variably detected in other AD populations.TH1 pathway activation is increased in some adults with chronic AD, and low activation levels are also reported in acute lesions and in some early-onset AD in children. Some Asian AD populations showed additional Th17 activation as well as in some early-onset pediatric AD.[16] Th22 is another pathway upregulated in AD. IL22 was shown to inhibit epidermal differentiation and thus promote barrier defects. The significance of these pathways will perhaps be revealed by studies of Th17 blockade (NCT02594098, clinicaltrials.gov) and the anti–IL-22 antibody fezakinumab (NCT01941537, clinicaltrials.gov) currently in phase 2 clinical trials.[37]

Ustekinumab, a fully human mAb approved for the treatment of psoriasis and psoriatic arthritis, binds to the common p40 subunit of IL-12/IL-23. These cytokines are produced by inflammatory myeloid cells and play a key role in the development of TH1 and TH17 cells.[37] In patients with AD, Weiss and colleagues[38] found that treatment with ustekinumab resulted in a significant decrease in the degree of epidermal hyperplasia/proliferation and the number of infiltrating dermal T cells, dendritic cells, and mast cells, and also they showed a reduction in TH2 and TH2-associated molecules. In a placebo-controlled, double-blind, phase 2 study in Japan, 79 adult patients with severe or very severe AD were randomized to ustekinumab 45 mg or 90 mg or placebo by subcutaneous injection at weeks 0 and 4. Neither of the 2 dosing regimens of ustekinumab resulted in significant improvement in the primary efficacy outcome of a percentage change in baseline Eczema Area and Severity Index (EASI) at week 12 versus placebo or improvement in major secondary efficacy end points.[39]

## JANUS KINASE INHIBITORS

Janus kinase (JAK) signal transducer and activator of transcription (STAT) is a common intracellular signaling pathway for many proinflammatory cytokines involved in

the pathophysiology of AD (eg, IL-4, IL-5, IL-13, IL-31).In mouse model studies of AD, JAK inhibitors have been shown to decrease IL-4, IL-5, IL-13, and IL-31 signaling and improve skin barrier functions. Various JAK inhibitors are being evaluated in early-phase human trials (listed in **Table 2**) for clinical efficacy. Tofacitinib is an oral small molecule JAK inhibitor approved for treatment of rheumatoid arthritis. Also, a topical formulation of tofacitinib has been shown to be beneficial for treatment of mild to moderate psoriasis. A phase II randomized trial of topical tofacitinib (2%) ointment used twice daily for 4 weeks showed significant improvement in EASI score in adults with mild to moderate AD compared with placebo.[40] Further trials of longer duration are needed, particularly because of the potential for immune suppression with JAK inhibitors.

### *Questions to Ask*

As more new and promising therapeutics become available, some hard question need to be answered. Are these drugs likely to be effective in all patients with AD or only certain AD phenotypes? How to select a specific biologic agent for a patient? Are there any good biomarkers or clinical markers to guide therapy? What is the long-term safety and efficacy? What is the risk of severe reactions? What is the safety/efficacy of drugs in younger children in whom the disease is more prevalent? How long to treat, and what is the likelihood of relapse after the treatment is stopped? What is the impact on other comorbid allergic diseases, such as asthma? When will these drugs be available for clinical use, and how about coverage by insurance payers?

## OTHER THERAPIES

### *Phototherapy*

Phototherapy is an efficacious treatment of AD and has been shown to reduce levels of inflammatory cells in the skin, reverse epidermal hyperplasia, and reverse thickening of the stratum corneum, thereby improving the skin barrier to entry of external antigens, and also decreasing skin bacterial infections, particularly by *S aureus*.[20,41] Phototherapy can be given as monotherapy or in combination with other topical or systemic treatments. Narrow-band ultraviolet B is usually preferred in the United States for long-term or maintenance therapy for chronic AD because of its low-risk profile, relative efficacy, availability, and provider comfort. Short courses of ultraviolet A can be recommended for exacerbations and for patients with severe, widespread AD. The Joint Task Force and the American Academy of Dermatology have published guidance documents for phototherapy for AD.[20] Phototherapy is not approved for children younger than 12 years of age in the United States. Phototherapy is a specialized treatment and is usually available in larger health centers, thus accessibility is sometimes a problem. Tanning beds are not a safe alternative. The most common side effects are cutaneous, including actinic skin damage, erythema, pigmentary skin changes, and tenderness. Systemic effects such as cutaneous melanoma or nonmelanoma skin cancer, photosensitive eruptions, and cataract are less common.[20]

### *Systemic Immunomodulatory Agents*

Systemic immunomodulatory agents are often considered in recalcitrant AD in both adult and pediatric patients unimproved with topical regimens and significant negative emotional and social impact.[20,42] Systemic corticosteroids are FDA approved to treat inflammatory skin disease, including severe, refractory AD, but only for a severe exacerbation and as a short-term bridge therapy, not for long-term daily maintenance

treatment.[20] The risks of serious side effects, rebound of the disease when stopped, and hypothalamic-pituitary axis suppression outweigh any potential benefits.

Cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil are all considered as off-label use for treatment of AD. Cyclosporine is a commonly preferred initial drug, followed by other drugs such as methotrexate or mycophenolate.[42] There are no consistent recommendations for dosing and treatment duration for these drugs because of insufficient data. Close monitoring for side effects and frequent blood testing are required.[20]

### *Anti–Immunoglobulin E Therapies*

IgE is a hallmark of atopic disease and IgE levels are remarkably increased in patients with extrinsic AD. Anti-IgE treatment has been explored. A systemic review of 26 studies involving 174 patients using variable protocols of dosing study designs failed to show evidence to support omalizumab to treat AD.[43] The investigators suggested a subset of patients with AD, possibly those with an urticarial component to their disease, might still benefit from this therapy. Anti-IgE blockade with omalizumab has shown efficacy in treating other atopic diseases such as chronic idiopathic urticaria and moderate to severe allergic asthma. This finding suggests that increased IgE level is an epiphenomenon of AD, perhaps mediating comorbidities such as food allergies, allergic rhinoconjunctivitis, and asthma, but not contributing to symptoms and inflammation.

### *Allergen Immunotherapy*

The Atopic Dermatitis Practice Parameter Update states that clinicians might consider allergen-specific immunotherapy (SIT) in selected patients with AD and aeroallergen sensitivity, but the data for this option are of limited quality.[44] SIT may be a treatment option for selected patients with proven sensitization to house dust and severe eczema that is not controlled with conventional therapies.

### *Probiotics, Prebiotics*

Slow development of *Bifidobacterium* species and *Lactobacillus* species has been seen in the gut microflora of allergic children. Consumption of probiotics has been shown to stimulate intestinal microbiota and suppress the TH2 response, leading to improvements in the balance between TH1and TH2. Probiotics, which are colonies of live microorganisms, or prebiotics, which are nondigestible oligosaccharides such as transgalactooligosaccharide and fructooligosaccharide, have been explored as prevention as well as for management of AD in many studies. A meta-analysis of 25 randomized controlled trials (n = 1599) studying the effectiveness of probiotics for treatment of AD were evaluated.[45] The primary outcome was significant differences in SCORAD (SCORing for Atopic Dermatitis) values favoring probiotics compared with the control. The significant value was seen in a group of children 1 to 18 years old (−5.74, 95% confidence interval−7.27 to −4.20), and in adults (−8.26, 95% confidence interval −13.28 to −3.25). However, the effectiveness of probiotics in infants (<1 year old) with AD was not proved. Treatment with a mixture of different bacterial species or of *Lactobacillus* species showed greater benefit than did treatment with *Bifidobacterium* species alone. Based on the review, the investigators suggested that probiotics could be an option for the treatment of AD, especially for moderate to severe AD in children and adults, but not in infants.[45] At this time, robust conclusions cannot be drawn, and more controlled studies are needed outlining dosage and species of probiotics benefiting patients with AD.

### *Cutaneous Microbiome*

Patients with moderate to severe AD are associated with decreased diversity of skin microbiota and increased colonization of *S aureus*. *S aureus* obtained from severe AD skin has been shown to upregulate IL-4, IL-13, and Il-22 expressions and also induce epidermal thickening and expansion of TH2 and TH17 cells in a mouse model more than from patients with milder AD and healthy controls.[46] Commensal bacteria such as *Staphylococcus epidermidis* and *Staphylococcus hominis* seen on healthy skin have been shown to be protective against *S aureus* because of production of antimicrobial peptides and to decrease its colonization in patients with AD.[47] Anti–IL-4/IL-13 treatment (dupilumab) in phase II trials has also been shown to decrease *S aureus* in lesional and nonlesional skin and thus reduce infections more than placebo.[27,28] Therefore possible benefits of using commensal strains of coagulase-negative *S epidermidis* and *S hominis* from healthy donors applied to AD skin, or spraying the commensal gram-negative coccobacillus *Roseomonas mucosa* on the arms of patients with AD (NCT03018275, clinicaltrials.gov) or targeted transplant lotion of coagulase-negative staphylococci applied to the arms of adults with AD are being investigated (NCT03151148, clinicaltrials.gov).

### *Dietary Supplements/Chinese Herbal Medicines*

Most studies, including meta-analyses, have failed to show a significant difference with active treatment using dietary supplements, including vitamins, fish oil, plant-derived essential fatty acids, primrose oil, and Chinese herbal medicines even though they have been used for long time as traditional remedies.[48,49]

### *Hospitalization/Multidisciplinary Approach*

Some patients with severe AD are best served in a multidisciplinary clinic or even in day-hospital settings. Such facilities provide an opportunity for comprehensive education and hands-on demonstration of wet wraps, bathing/soaking, and topical treatments. This process may help identify triggers and stress, provide the services of nutritionists and behavioral therapists to address itch-scratch cycles and stress, and provide access to specialists including dermatologists and allergists in a single platform to improve outcomes.[50]

## SUMMARY

AD is a complex systemic inflammatory disease. Long-standing topical therapies are not sufficient for treating severe AD or to improve quality of life. Systemic immunomodulating agents are limited by side effects and by their effectiveness. Targeted new therapies promise to be more effective and to maintain improvement with fewer side effects.

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