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Atopic Dermatitis: A Review of Diagnosis and Treatment

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Atopic dermatitis, more commonly known as atopic eczema, is a chronic, relapsing inflammatory skin disorder characterized by dry skin, localized erythematous rash, and intense pruritus. The clinical manifestations are variable and age dependent. As one of the most common skin disorders globally, atopic dermatitis poses a significant clinical and economic burden on affected patients. Individual treatment strategies are imperative in improving patient outcomes and reducing these burdens. Recent advances in understanding the genetic, immunologic, and environmental factors influencing atopic dermatitis have opened avenues for novel treatment modalities. This article highlights the clinical presentation, pathophysiology, diagnosis criteria, as well as current recommendations on treatment of atopic dermatitis.

ABBREVIATIONS AA, allergic asthma; AD, atopic dermatitis; AIT, allergen immunotherapy; AR, allergic rhinitis; FA, food allergy; FDA, US Food and Drug Administration; FTU, fingertip unit; Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; NBUVB, narrowband ultraviolet B; NMA, network meta-analysis; PDE-4 inhibitor, phosphodiesterase-4 inhibitor; RCTs, randomized controlled trials; TB, tuberculosis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Th, T-helper; WHO, World Health Organization; WWT, wet wrap therapy

KEYWORDS allergic eczematous dermatitis; allergy; atopic dermatitis; atopic eczema; biologics; Jak kinases; small molecule therapies

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Introduction

Atopic dermatitis (AD), more commonly known as atopic eczema, is a chronic, relapsing inflammatory skin disorder characterized by dry skin, localized erythematous rash, and intense pruritus. Atopic dermatitis is one of the most common chronic inflammatory skin disorders, affecting approximately 220 million people worldwide according to the data collected by the WHO (World Health Organization) Global Burden of Diseases Initiative.[1] Originally viewed as a skin disorder of childhood, AD has an estimated prevalence of 20% in children and 10% in adults.[2–7] The burden of disease ranks number one among nonfatal skin diseases globally, significantly impairing the quality of life of affected individuals and their families.[8–10]

The clinical phenotype of AD is heterogeneous, punctuated by flares and remissions of dermatitis on a background of dry, sensitive skin.[11] For most patients, AD develops during childhood and is triggered by irritants, allergens, and microbes. Some patients outgrow their condition by adolescence, while others experience localized recurrences after longer periods of resolution in adulthood. In rare instances, AD can also develop later in adult life.[3,4] The morphology and distribution of AD is age dependent. With chronic or relapsing disease and repeated scratching, the skin becomes thickened or lichenified.[11]

There is no single cause of atopic dermatitis. The etiology is complex involving an interplay between genetics, impaired epidermal skin barrier, dysregulated immune system, and altered skin microbiome.[12–14] Although the exact mechanisms causing these abnormalities are not fully elucidated, AD may affect organs beyond the skin. In fact, AD is more recently regarded as a systemic disorder associated with increased risks of developing both allergic and nonallergic comorbidities.[15–17]

The management of AD should be individualized, based on the severity and extent of cutaneous lesions, while considering patient preferences as well as medication costs and adverse effects. General measures for all patients include trigger avoidance, enhancing skin barrier function and skin hydration with moisturizers/emollients, education on proper medication use and adherence, and controlling pruritus and acute flares. The mainstay of treatment includes topical anti-inflammatories. In severe or refractory disease, novel biologics, small molecules, and other systemic immunosuppressive medications may be warranted.[18]

A focused literature search was conducted to provide a nonsystematic review that aims to deliver an overview on the clinical presentation, pathophysiology, diagnosis criteria, as well as current guidelines on treatment of AD.

Pathogenesis

The pathogenesis of AD is complex and involves exposures to environmental triggers in genetically predisposed individuals. A dysfunction in the epidermal barrier has been considered the first step in the development of AD, although it can be secondarily disrupted by inflammation or trauma from scratching.[5,6,12–14] The strongest genetic risk factor associated with AD is mutations in the filaggrin gene (*FLG*), resulting in a deficiency in filaggrin, an essential structural protein involved in maintaining the integrity of the epidermal skin barrier. Impaired protein synthesis in the skin results in decreased lipid content, increased transepidermal water loss, and excessive dryness. The disrupted skin barrier increases the permeability to irritants, allergens, and microbes and increases the production of proinflammatory cytokines.[5,6,12–14] However, mutations in filaggrin are not sufficient in causing AD alone, and other gene mutations encoding structural and/or functional proteins of the skin as well as genes that regulate the innate and adaptive immune system have been identified.[19]

Dysregulation of both the innate and adaptive immune responses are involved in pathogenesis of AD.[5,6,12–14] Characteristic of AD, there is predilection for CD4+ lymphocytes to differentiate toward a T-helper (Th) 2 lineage. In acute lesions, keratinocytes release proinflammatory cytokines including interleukin (IL) 25, IL-33, and thymic stromal lymphopoietin, which stimulate cutaneous antigen-presenting cells to activate Th2 cells, and to some extent, Th22 and Th17 subsets. Th2 cells produce inflammatory cytokines, including IL-4, IL-5, IL-13, IL-31, and IL-33, causing skin barrier dysfunction; impair keratinocyte differentiation; and produce itch symptoms. In addition, there is decreased antimicrobial production by keratinocytes, contributing to the increased susceptibility to cutaneous bacterial and viral infections. Cytokines IL-4, IL-5, and IL-13 also stimulate antibody class switching to immunoglobulin (Ig) E and promote eosinophil activation in the blood and peripheral tissue. It should be noted that IgE is not directly implicated in the pathogenesis of AD. Chronic AD is characterized by a mixed T-cell phenotype; there is further augmentation of Th2 cells, and additional recruitment of Th1, Th22, and Th17 subsets, which results in epidermal thickening and abnormal keratinocyte proliferation.[5,6,12–14]

The skin in AD also exhibits differences in microbiome when compared with healthy individuals.[5,6,12–14] Whether these changes contribute to the primary pathology, or occur secondarily as a result of damaged skin, is unclear. The skin microbiota function as part of the epidermal barrier and also modulates the host immune system to pathogens. Compared with healthy skin, AD demonstrates reduced diversity of typical commensal organisms, and an increased colonization of pathogenic bacteria, especially *Staphylococcus aureus*. In fact, *S.aureus* colonizes about 90% of patients with AD, which contributes to the development and exacerbation of AD through mechanisms acting on keratinocytes and immune cells.[20]

How Does the Clinical Course of Atopic Dermatitis in Childhood Progress?

Atopic dermatitis can manifest anytime in life, but most cases begin in childhood. It is estimated that AD develops within the first 6 months of life in 45% of affected individuals, and 80% to 90% will develop AD by the age of 5 years.[5,6,11] The disease is chronic with persistent or relapsing and remitting patterns. Previous literature has demonstrated that 80% of cases did not persist beyond 8 years of age; however, an inadequate length of follow-up may have limited such results.[21] More recently, a systematic review and meta-analysis of studies found no significant differences in the prevalence of AD before and after childhood.[3] Thus, the proportion of individuals experiencing persistent or adult-onset symptoms or relapses following extended asymptomatic periods is considerably greater than previously estimated, emphasizing that AD is a lifelong condition characterized by variable phenotypic manifestations.[5]

The clinical morphology and distribution of AD is age dependent although any area can be affected.[5,6,11] Diffuse disease can occur in the most severe cases. The hallmark of AD is intense pruritus, often accompanied by excoriated skin. Acute dermatitis predominates in infantile AD (younger than 2 years) and is characterized by edematous, erythematous papules and plaques with vesiculation, weeping, and serous crusting. Typical lesions are distributed over the cheeks (with sparing of the central face), scalp, neck, extensor extremities, and trunk, while usually sparing the diaper area. In childhood AD (2–12 years old) and adolescent AD (12–18 years old), the lesions become chronic, characterized by thickened and scaly plaques with less exudate and erythema. The classic sites of involvement are the flexural extremities including the antecubital and popliteal fossa. Other common areas include eyelids, hands, feet, and neck.[11] The skin of affected individuals is typically diffusely dry and described as sensitive.

What Is the Clinical Course of Atopic Dermatitis in Adulthood?

Adult pruritic dermatitis (>18 years old) can be the first manifestation of AD, or persistent or remitting disease from childhood. In fact, approximately 25% of adult AD cases develop the condition for the first time in later years.[3,8,22] The morphology and distribution tend to emulate those of adolescent AD, that is, plaques of chronic dermatitis that can be diffusely distributed or localized to the flexural folds, hands, and eyelids. Adults may have isolated subtypes of AD such as chronic hand dermatitis, nipple dermatitis, or head-and-neck dermatitis localized to the scalp, shoulders, and upper chest.[5,11,22] Patients who have had AD from childhood

are more likely to have extensive disease that is refractory to treatment.[11]

What Are the Exacerbating Factors in Atopic Dermatitis?

There are many factors that can aggravate AD and lead to worsening symptoms. Knowledge of these factors is important to combat them. Typical aggravating factors of AD include irritant dermatitis, skin infections, food allergy (FA) in children, and stress in adults.[23,24] Many irritants, allergens, and microbes can easily penetrate the skin owing to the decreased skin barrier seen in AD. Many nonspecific irritants encountered daily include changes in temperature or humidity, cigarette smoke or air pollutants, sweat, friction from clothing, fabrics such as wool as well as a variety of soaps, detergents, and cosmetics. Physical trauma from scratching is also an important cause of AD exacerbations. Known as the scratch-itch cycle, damage to keratinocytes from scratching can perpetuate inflammation and cytokine release that promote further itching. Atopic dermatitis skin has an increased susceptibility to bacterial and viral infections, which can trigger and exacerbate lesions. Lastly, FAs and aeroallergens can induce the symptoms of AD. Contact allergy can result in atypically distributed and refractory AD. Avoidance of certain allergens may be used as adjuvant to treatment in AD.[24]

What Are the Histologic Characteristics of Atopic Dermatitis?

Eczema is a wastebasket term for acute dermatitis that is characterized histologically by spongiosis or intercellular edema. The microscopic findings of AD are nonspecific and share many features with other eczematous rashes. Histology is more useful in characterizing the chronicity of eczematous lesions as acute, subacute, or chronic. In instances where the diagnosis remains unclear, skin biopsy can also aid in excluding other inflammatory dermatoses.

The hallmark of AD is characterized by spongiosis, with intraepidermal fluid collection and widening of intercellular spaces.[11,25] With further accumulation of fluids there is disruption of adhesion molecules and formation of microvesicles. Dermal changes include edema and superficial perivascular infiltration of lymphocytes, with occasional eosinophils. In subacute lesions, spongiosis becomes less evident and the skin becomes thickened, as demonstrated by acanthosis and hyperkeratosis. Spongiosis is absent in chronic dermatitis and no vesiculation is present; skin thickening becomes more pronounced and the dermis may have fibrotic changes.[11,25]

What Is the Atopic March?

Atopy is the genetic predisposition to develop allergic disease. The atopic march refers to the sequential development of allergic disease that occurs with aging. The common sequence of the atopic march includes AD, FA, allergic asthma (AA), and allergic rhinitis (AR). Atopic dermatitis is typically the starting point for allergic disease, and the risk of developing FA, AA, and/or AR increases with earlier onset and more severe AD.[15,16] Indeed, patients with AD are at greater risk of developing allergic comorbidities than those without. It has been hypothesized that sensitization of various allergens occurs transcutaneously as a result of the disrupted skin barrier in AD, which increases the risk of FA, AA, and AR.[15] Thus, early epidermal barrier protection and treatment of AD may halt the progression of atopic march later in life.

What Are 3 Major Diagnostic Criteria of Atopic Dermatitis Based on the Hanifin-Rajka Model?

The diagnosis of AD remains clinical and based on historical and clinical features, typical morphology and distribution of skin lesions, and exclusion of other dermatoses. Various diagnostic criteria have been proposed to aid in the diagnosis of AD.[26–28] According to the Hanifin-Rajka criteria, a diagnosis of AD requires the presence of at least 3 of the following 4 major clinical features: pruritus, typical morphology and distribution of skin lesions, chronically relapsing course, and personal or family history of atopy.[26] Pruritus is a hallmark of AD and the diagnosis should be reconsidered in its absence.

What Are Some Minor Diagnostic Criteria for Atopic Dermatitis?

In addition to the major characteristics, the Hanifin-Rajka model requires 3 out of 23 minor criteria for diagnosis, which can be cumbersome in clinical practice.[26] Moreover, many of the criteria have been challenged. Some of the minor criteria have been found to be nonspecific for AD, whereas others are specific for AD but uncommon. More recently, the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Joint Task Force and the American Academy of Dermatology have published guidelines on the diagnosis of AD.[27,28] Both guidelines list associated features that can help suggest but are not required for the diagnosis of AD. Some of the associated features include xerosis (dry skin), ichthyosis, palmar hyperlinearity, keratosis pilaris, atypical vascular changes (facial plethora, perioral pallor, white dermographism, delayed blanch), infraorbital fold, ocular changes (keratoconus, anterior subcapsular cataracts), nipple eczema, cheilitis, susceptibility to cutaneous infection (especially *S aureus* and herpes simplex) and impaired cell-mediated immunity, immediate (Type I) skin test response, and early age of onset.

How Can One Classify the Severity of Atopic Dermatitis?

The severity of AD is based on the features and extent of skin involvement, the presence of comorbidities, the amount of medication required for control, the intensity of pruritus and its effect on sleep and quality of life. Severity can be classified as mild, moderate, and severe as follows:

Mild: Infrequent itching, areas of dry skin (with or without small areas of redness). Little impact on daily life/sleep and psychological well-being;

Moderate: Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening), moderate impact on daily living and psychological well-being;

Severe: Widespread dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and change in pigmentation). Severe limitation on daily activities and psychological well-being.

What Are Some Treatment Modalities Currently Used in Atopic Dermatitis?

General Management of AD. Atopic dermatitis is a lifelong disease. While some individuals experience persistent symptoms, many go through periods of exacerbation (or flares) followed by periods of remission. The course of the disease varies from person to person, necessitating an individualized approach that takes into account both patient-specific factors such as age and adherence, as well as disease-related factors like the extent and distribution of symptoms and whether the condition is in an acute flare or persistent state. The goal of treatment is complete or partial resolution of cutaneous inflammation, control of pruritus, and prevention of future flares. Treatment for AD is separated into 2 phases: 1) induction of remission, which refers to the treatment of uncontrolled active disease or flares; and 2) maintenance of remission or proactive therapy, which refers to intermittent therapy to treat subclinical inflammation and prevent a future flare.[18,29] This treatment strategy may modify the natural course and prevent future atopic comorbidities.[30] A stepwise approach can be followed for disease of increasing severity or refractory disease. Topical therapy represents the mainstay of both induction and maintenance of remission for mild to moderate disease. For severe, widespread disease or patients whose condition remains poorly controlled despite maximum topical therapy, advancement to systemic therapy is often required. After ensuring a correct diagnosis of AD, refractory disease should always prompt evaluation for patient adherence, irritant and allergen avoidance, and comorbid conditions (infection and contact dermatitis) before issuing new therapy. Confirmation is needed to ensure that uncontrolled disease is a result of AD and to improve patient outcomes.

Patient Education. Lack of information and confidence in medical treatment leads to poor outcomes. Hence, patient education is vital to the development of skills required to manage AD. Most studies on patient education demonstrate a positive impact in patients' clinical outcomes and quality of life. Patients and family members should be aware that there is no cure for AD; treatment may be lifelong, reflecting the chronic nature of their disease. Knowledge of appropriate treatment options including efficacy and safety profile, and clear goals of management, is important to reduce fear and increase treatment compliance. All patients should be provided with written information that includes general disease information, trigger avoidance, detailed skin care recommendations and treatment plans to facilitate adherence and reduce phobias. Online educational resources are available through organizations such as the National Eczema Association (nationaleczema.org).

Basic Skin Care. Regardless of AD severity, nonpharmacologic skin care measures should be implemented for all patients. These basic measures include daily bathing, frequent skin moisturization, and avoidance of potential triggers.

Baths aid in skin hydration and cleaning the skin of exogenous irritants, microbes, and allergens that can provoke flares. They also have a soothing effect and reduce pruritus. Baths should be limited to 5 to 10 minutes with limited use of neutral pH, fragrance-free hypoallergenic soaps or non-soap cleansers to reduce irritation and damage to the skin. Several bathing additives may be beneficial adjunctive therapies for AD.[31] Bleach baths, through their antimicrobial and direct anti-inflammatory effects, demonstrate a minor improvement in AD severity and are recommended as adjuvant therapy for moderate to severe AD.[18,32] Use is limited to 10 minutes per bath and can be performed 2 to 3 times per week. Bleach baths are formed by adding ½ to ¼ cup of concentrated household bleach (5.25% sodium hypochlorite) to a half full to full bathtub of water, respectively. Patients should be aware that the bleach bath recipe has the same level of chlorine in your average swimming pool to reduce fears.

Bathing should be followed by the immediate (within 3 minutes) use of moisturizer to improve the epidermal skin barrier and decrease transepidermal water loss. Moisturization is a cornerstone of treatment for AD and has been shown to reduce AD severity and topical prescription use, while increasing time between flares.[33] Indeed, moisturizing may be sufficient to control AD in the mildest cases. Various different moisturizers exist (occlusive, emollients, humectants) and are produced in multiple vehicle types (e.g., ointments, creams, lotions), which can create confusion for patients. In general, ointments are the most occlusive and exert a strong emollient effect, but are limited by their greasy texture, whereas creams are less occlusive, but they are more

tolerable for patients. A randomized controlled trial (RCT) comparing different types of moisturizers found no difference between the 4 types of vehicles and suggests that the best moisturizer is one that is consistently used.[18,34] Based on expert consensus, over-the-counter occlusive, bland moisturizers (fragrance-free and hypoallergenic) are preferred.[18] Moisturizers should be applied at least once daily, ideally right after bathing, and titrated to symptomatic benefit.

Recognition and avoidance of aggregated factors plays a crucial role in the management of AD by reducing the frequency and severity of flares. Many AD triggers exist such as irritants, infections, temperature, aeroallergens, and food allergens (see exacerbation factors above). Patients are advised to identify and avoid common triggers that can exacerbate their symptoms. Identification of allergic triggers may be confirmed with skin prick testing, *in vitro* testing for specific IgE antibodies, and patch testing. Skin infections should be treated appropriately with topical or systemic antibiotics. The regular use of topical antimicrobials is not recommended unless clinical suspicion of superimposed infection exists.[18]

Approach to Mild to Moderate AD. With AD being immune mediated, most patients require treatment with anti-inflammatories despite the use of skin hydration and moisturization. Topical anti-inflammatories are the preferred treatment option for both acute flares and maintenance of remission for mild to moderate AD. Prescription topical anti-inflammatories include topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), topical phosphodiesterase-4 (PDE-4) inhibitors, and oral Janus kinase (JAK) inhibitors (Table 1). In mild disease, topical therapy may be used reactively as needed for flares followed by maintenance treatment with emollients alone. For moderate AD, induction of remission is followed by proactive therapy to increase the time between flares. When considering patient values and medication adverse effects, clinicians might opt to use multiple agents for patients to target different levels of AD severity or application at different body sites. Patients should be aware that topical treatments may take time and involve a trial-and-error process. Patients should be reevaluated every 2 to 4 weeks to monitor drug efficacy during flares. The persistence of signs and symptoms of AD after an adequate trial of an appropriate potency medication should prompt advancement in treatment. With each clinic visit, patients should be reassessed for medication adherence and adverse events, trigger avoidance, and associated comorbidities.

Topical Corticosteroids. Topical corticosteroids are recommended first-line therapies for both acute flares and intermittent maintenance therapy of AD.[18,35] They exert a pleiotropic effect on the immune system by reducing inflammation and immune function. Numerous clinical studies have demonstrated the efficacy of TCSs in AD. In a network meta-analysis (NMA) of 219 RCTs, TCSs were among the best treatments at improving AD severity, reducing pruritus, and achieving long-term control of AD.[36]

Topical corticosteroids can be clinically classified by potency into 4 main categories: low potency (groups 6–7), medium potency (groups 5–4), and high and super high potency (groups 2–3 and group 1, respectively) (Table 2). The selection of a specific TCS is dependent on the location, thickness, and severity of skin lesions as well as patient age, preference, and cost. In general, short courses of medium- or higher-potency TCSs are used to rapidly control acute flares over days to weeks. In fact, TCS group 1 is the best at improving AD severity, while groups 2 to 5 are the best at improving itch.[36] Low-potency TCSs are generally preferred in thin skin sites (face, genitals, folds) and in children because of the increased risk of adverse effects and systemic absorption. However, limited use (≤4 weeks) of higher-potency TCSs may be necessary in severe, recalcitrant flares, even in infantile AD. Following clearance, TCSs are tapered to a low- to medium-potency TCS as proactive therapy applied to previous lesional skin. TCS group 5 is ranked the best to maintain long-term AD control.[36]

Expert consensus recommends medium- to high-potency TCSs be used once daily by patients for acute flares.[18] Twice-daily TCS is common practice, but there is evidence that once daily is sufficient.[37,38] For all patients, the lowest effective dose of TCS should be used for the minimum duration to attain disease control. It is important to avoid undertreatment to prevent suboptimal outcomes and patient frustration. For long-term maintenance therapy, it is recommended that medium-dose TCS (groups 3–5) be used once daily on 2 consecutive days per week (usually the weekends).[18,37] Patients should be instructed on how to estimate the amount of TCS needed to achieve adequate control of lesions. A fingertip unit (FTU) is the amount of medication squeezed from a standard 5-mm nozzle over a distance from the tip of the index finger to the crease of the distal interphalangeal joint. One FTU is enough to cover the 2 adult hands or 2% body surface of an adult and is equivalent to 0.5 g of medication.[39]

Topical corticosteroids are well tolerated and the adverse events are low.[36,37,40–43] There is a lack of studies evaluating the long-term use of high-potency TCSs; however, this practice is generally avoided. Common side effects include skin atrophy, telangiectasia, striae, purpura, perioral dermatitis, and acneiform or rosacea-like eruptions.[27,39,41] The risks are greatest with higher-potency TCSs, prolonged duration of use, thinner skin, skin occlusion, and extremes of age. Less common side effects include dyspigmentation, focal hypertrichosis, delayed wound healing, and exacerbation of skin infections. Contact sensitization to the steroid molecule can occur in a minority of patients, but many

Table 1. Summary of Recommended Therapies Used for Atopic Dermatitis.[18,29,36,39–47]

Medication	Mechanism of Action	Administration, Dosage	Adverse Effects, Contraindications, Drug Monitoring	Notes
Topical Corticosteroids				
Corticosteroids	The anti-inflammatory effects of corticosteroids include vasoconstriction, decreased production of prostaglandins and leukotrienes (via inhibition of phospholipase A2), decreased expression of proinflammatory genes, and increased expression of anti-inflammatory genes. Corticosteroids also suppress the maturation, differentiation, and proliferation of immune cells	1 FTU = 2 hands = 2% BSA = ~0.5 g Acute flare: mid- to high-potency once daily for 2–4 wk Proactive therapy: low to medium potency once daily on weekends	The most common local adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura. Less common side effects are delayed wound healing and exacerbation of infections. Systemic adverse effects are rare; however, prolonged use of high-potency steroids can lead to suppression of the hypothalamic-pituitary-adrenal axis and lead to manifestations of Cushing syndrome	First-line therapy for flares and maintenance of mild to moderate AD Wet wrap therapy, bleach baths, and AIT can aid in control of flares refractory to topical therapy alone
Topical Calcineurin Inhibitors				
Tacrolimus, pimecrolimus	FK506-binding proteins that inhibitor calcineurin and hinder the activation of T cells and the synthesis and release of proinflammatory cytokines	Tacrolimus is available as 0.03% and 0.1% ointments Pimecrolimus is available as a 1% cream Acute flares: applied once daily for 6 wk Proactive therapy: once daily 2–3 times per wk	The most frequent adverse effect is transient, localized burning, stinging, and itching. Reduce by positive framing, precooling medication, pretreatment with TCS The FDA black box warning linking TCI with an increased risk for cancer	Tacrolimus is approved for moderate to severe AD: 0.03% for ≥2 yr/o, 0.1% ≥16 yr/o. Used off label for all ages Pimecrolimus is approved for mild to moderate AD in ≥2 yr/o May be considered an alternative first-line therapy for AD flares in sensitive sites, for long-term persistent therapy, or for proactive therapy
PDE-4 Inhibitors				
Crisaborole	A PDE-4 inhibitor that inhibits intracellular degradation of cAMP, which regulates both pro- and anti-inflammatory cytokine synthesis, T-cell activation, and antigen presentation	Apply a thin film of 2% ointment to affected areas twice daily. When clinical response is achieved, dosing can be reduced to once daily	The most common adverse effect is application site pain, burning, and stinging. Keeping the medication refrigerated and applying it cold can reduce the stinging sensation	FDA approved for the treatment of mild to moderate AD in adults and children 3 mo of age or older. TCS and TCI preferred over topical PDE-4s

(Table cont. on page 593)

Table 1. Summary of Recommended Therapies Used for Atopic Dermatitis.[18,29,36,39–47] *(cont.)*

Medication	Mechanism of Action	Administration, Dosage	Adverse Effects, Contraindications, Drug Monitoring	Notes
Biologics				
Dupilumab, tralokinumab	Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 cytokine-induced inflammatory responses Tralokinumab is a human monoclonal IgG4 antibody that binds and inhibits the activity of IL-13, blocking its interaction with the IL-13 receptor α1 and α2 subunits	Dupilumab dosing: ≥18 yr/o: 600-mg loading dose followed by a maintenance dose of 300 mg every other wk 6–17 yr/o dosing is weight based: ≥60 kg: 600-mg loading dose followed by 300 mg every other wk 30 to <60 kg: 400-mg loading dose followed by 200 mg every other wk 15 to <30 kg: 600-mg loading dose followed by 300 mg every 4 wk 6 mo–6 yr/o: no loading dose: 15 to <30 kg: 300 mg every 4 wk 5 to <15 kg: 200 mg every 4 wk Tralokinumab dosing: ≥18 yr/o: 600-mg loading dose, followed by 300 mg every other wk 12–17 yr/o: 300-mg loading dose followed by 150 mg every other wk	Common adverse effects are injection-site reactions and mild conjunctivitis (treat with eye drops)	First line for moderate to severe AD refractory, intolerant, or unable to use medium- or higher-potency topical therapies. Approved for ages ≥ 6 mo Injected subcutaneously into the thigh, low abdomen, or upper arm May consider tapering dose to every 3 or 4 wk if disease is in remission for ≥6 mo
Oral JAK inhibitors				
Upadacitinib, abrocitinib,	Upadacitinib and abrocitinib are small molecules that reversibly inhibit the enzyme JAK1, preventing signaling of IL-4, IL-13, and other cytokines involved in the pathogenesis of AD	Upadacitinib: 15-mg tablet once daily. For insufficient response, the dose can be increased to 30 mg daily. For eGFR 15 to <30 mL/min: 15 mg once daily. Use is not recommended for those with eGFR <15 mL/min Abrocitinib is administered as a 100-mg tablet daily. For insufficient response after 12 wk, the dose can be increased to 200 mg daily. For eGFR 15 to <30 mL/min: 50 mg once daily. For insufficient response after 12 wk, the dose can be increased to 100 mg daily. Dose reduction recommended with CYP2C19 inhibitors	Common side effects include upper respiratory infections, nasopharyngitis, nausea, headache, acne (mild and can be treated with a topical retinoid) Oral JAK inhibitors have a black box warning for increased risk of serious infections, malignancies, major adverse cardiovascular events, thrombosis, and all-cause mortality Requires lab monitoring: CBC, CMP, lipids before starting and every 3 mo. Screen for TB (annually), HIV, viral hepatitis	Upadacitinib and abrocitinib are second-line therapies for treatment of moderate to severe AD when not controlled by other systemic therapies (including biologics) or use is inadvisable. Approved in ≥12 yr/o Clinically useful for short-term use as a bridge to other therapies, for a severe flare, or for social circumstances, as they work rapidly, often within days

(Table cont. on page 594)

Table 1. Summary of Recommended Therapies Used for Atopic Dermatitis.[18,29,36,39–47] *(cont.)*

Medication	Mechanism of Action	Administration, Dosage	Adverse Effects, Contraindications, Drug Monitoring	Notes
Other Immunosuppressive Agents				
Cyclosporine	Cyclosporine inhibits the production and release of IL-2, thereby inhibiting the activation of T lymphocytes	2.5–3.5 mg/kg/day divided into 2 doses for ≤16 wk. Once symptom improvement has been achieved, the dosage can be gradually tapered by 0.5 to 1 mg/kg/day every 2 wk. Limit use to 1–2 yr	Common side effects include hypertension and nephrotoxicity. Other side effects are diabetes, hepatotoxicity, hirsutism, gingival hyperplasia, neurotoxicity, increased risk of infection, and malignancy Requires lab monitoring: blood pressure, CBC, CMP every 2 wk for the 1–2 mo and then every 1–3 mo	Used off label for moderate to severe AD that is refractory, intolerant, or unable to use mid- to high-potency topical treatments and other systemic therapies inclusive of a biologic

AD, atopic dermatitis; AIT, allergen immunotherapy; BSA, body surface area; CBC, complete blood count; CMP, complete metabolic panel; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; FTU, fingertip unit; IgG4, serum immunoglobin G4; IL, interleukin; JAK, Janus kinase; PDE-4, phosphodiesterase-4; TB, tuberculosis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids; yr/o, year old

cases result from preservatives or other components of the vehicle. There is a risk of cataracts and glaucoma development with periocular use of TCSs. Systemic toxicity is rare and may include adrenal suppression and Cushing syndrome.

Special considerations are required during TCS use for infantile AD. Children younger than 2 years have a higher ratio of body surface area to body weight. This leads to increased absorption of TCSs, which may cause increased adverse events. As a result, few TCSs are licensed for infants. However, off-label use of medium- to high-potency TCSs may sometimes be required to treat thick lesions on the cheeks of infants. It is important to stress to patients and caregivers that TCSs are safe when used properly and there is greater harm associated with undertreatment than for potential adverse effects. Patient education and reassurance regarding the safety profile of TCSs may help combat the high rates of steroid phobia and improve the chances of successful outcomes.[44]

Topical Calcineurin Inhibitors. The TCIs tacrolimus and pimecrolimus are nonsteroidal, topical anti-inflammatories that block T-cell activation and production of proinflammatory cytokines. TCIs have demonstrated efficacy in reducing pruritus and severity of AD and are used as second-line agents for the treatment and prevention of AD flares.[36]

Tacrolimus is available as 0.03% and 0.1% ointment and both are approved for the treatment of moderate to severe AD, although used frequently in milder disease. Tacrolimus 0.03% is approved for use in ages 2 years and older, while tacrolimus 0.1% is approved for use in ages 16 years and older.[45] Pimecrolimus 1% cream is approved for the use of mild to moderate AD in ages 2 years and older. TCIs are commonly used off-label in infants, as large clinical trials have demonstrated safety and efficacy in the pediatric population.[46]

TCIs are typically applied twice daily to affected areas during flares; however, once-daily use may be appropriate.[18] For maintenance therapy, application of a TCI 2 to 3 times weekly is sufficient in preventing flares. Patients should be instructed to apply the smallest amount required to cover the affected area.

TCIs are recommended as alternative agents to TCSs in the treatment of AD.[18,35] Compared with TCSs, TCIs are not associated with skin atrophy. In turn, TCIs can be beneficial for chronic AD when continuous therapy is required as well as for use in sensitive sites, a concern for the atrophogenic potential of TCSs. In regard to efficacy, tacrolimus is equal in strength to medium-potency TCSs (group 4–5), and pimecrolimus is comparable in efficacy to a low-potency TCS (group 5–6).[18,36] As proactive agents, TCIs are among the best agents in reducing the number of flares.[36]

Adverse effects are limited to transient burning, stinging, erythema, and pruritus at the sites of application. Tacrolimus 0.03% or pimecrolimus 0.1% are generally better tolerated than tacrolimus 0.1%. Positive framing

Table 2. Topical Therapies Used for Atopic Dermatitis

Topical Steroids + Therapy			
Brand Name	**Generic Name**	**Medium**	**Available Sizes**
Potency	**Ultra High – I**	**I**	
Diprolene	Betamethasone dipropionate (augmented) 0.05%	G, O	15, 45, 50 g
Clobex	Clobetasol propionate 0.05%	L, Sh	59, 118 mL (L): 118 mL (Sh)
Olux		F	50, 100 g
Temovate		C, G, O	15, 30, 45 g (C): 15, 30, 60 g (G)
Temovate E		C	15, 30, 60 g
Apexicon	Diflorasone diacetate 0.05%	O	15, 30, 60 g
Vanos	Fluocinonide 0.1%	C	30, 60 g
Cordran	Flurandrenolide 4 mcg/m^2	T	24" × 3" and 80" × 3" rolls
Ultravate	Halobetasol propionate 0.05%	C, O	15, 50 g
	High – II		
	Amcinonide 0.1%	O	15, 30, 60 g
Diprolene	Betamethasone dipropionate (augmented) 0.05%	L	30, 60 mL
Diprolene AF		C	15, 50 g
Diprosone	Betamethasone dipropionate 0.05%	O	15, 45 g
Topicort	Desoximetasone 0.25%	C, O	15, 60 g
	Desoximetasone 0.05%	G	15, 60 g
Apexicon E	Diflorasone diacetate 0.05%	C	15, 30, 60 g
Lidex	Fluocinonide 0.05%	C, G, O	15, 30, 60 g
Halog	Halcinonide 0.1%	C, O, So	15, 30, 60, 240 g (C, O): 15, 30, 60 mL (So)
	Medium-High – III		
Cyclocort	Amcinonide 0.1%	C	4, 15, 30, 60 g
Betanate	Betamethasone dipropionate 0.05%	C	15, 45 g
Cutivate	Fluticasone propionate 0.005%	O	15, 30, 60 g
Cinalog	Triamcinolone acetonide 0.5%	C, O	15 g
	Medium – IV-V		
Beta-Val 0.1%	Betamethasone valerate	C, L	14, 45 g (C); 60 mL (L)
Luxiq 0.12%		F	100 g
Topicort LP	Desoximetasone 0.05%	C	15, 60 g
Synalar	Fluocinolone acetonide 0.025%	C, O	15, 60 g
Cutivate	Fluticasone propionate 0.05%	C	15, 30, 60 g
Locoid	Hydrocortisone butyrate 0.1%	O	5, 10, 15, 30, 45 g
Pandel	Hydrocortisone probutate 0.1%	C	15, 45, 80 g
Westcort	Hydrocortisone valerate 0.2%	C, O	15, 45, 60 g (C, O): 120 g (C)

(Table cont. on page 596)

Table 2. Topical Therapies Used for Atopic Dermatitis *(cont.)*

Topical Steroids + Therapy			
Brand Name	**Generic Name**	**Medium**	**Available Sizes**
Elocon	Mometasone furoate 0.1%	C, L, O	15, 45 g (C, O): 30, 60 mL
Kenalog	Triamcinolone acetonide 0.025%	C, L, O	15, 80, 454 g (C, O): 60 mL
Triderm	Triamcinolone acetonide 0.1%	C, L, O	15, 80, 454 g (C, O): 15, 60 mL
	Low – VI		
Aclovate	Alclometasone dipropionate 0.05%	C, O	15, 45, 60 g
Desonate	Desonide 0.05%	G	15, 30, 60 g
Desowen		C, O	15, 60 g
Lokara		L	60, 120 mL
Verdeso		F	100 g
	Fluocinolone 0.01%	C	15, 60 g
Locoid	Hydrocortisone butyrate 0.1%	C	5, 10, 15, 30, 45 g
	Least – VII		
	Hydrocortisone 1%, 2.5%	C, L, O	20, 30, 120 g (C, O): 60, 120 mL (L)
Other Topical Medications			
Tacrolimus	0.03% -> 2 yr/o, 0.1% -> 16 yr/o BID	More potent	
Pimecrolimus	1% BID	Less potent	
Eucrisa	Crisaborole 2% BID		

C, cream; F, foams; G, gels; L, lotion; O, ointment; Sh, shampoo; So, solution; T, tape; yr/o: year old

of potential sensations has shown to increase the willingness to tolerate application discomfort.[47] In addition, precooling the TCI tube by refrigerating for 15 to 20 minutes and/or pretreatment with TCS may reduce irritation before introducing a TCI.[18] TCIs have a black box warning regarding the increased risk of malignancy because of the cancer risk of systemic tacrolimus in immunosuppressive doses. This associated has not been demonstrated in subsequent large studies.[48]

Topical Crisaborole. Crisaborole topical ointment is a nonsteroidal anti-inflammatory PDE-4 inhibitor approved in the United States to treat mild to moderate AD in patients 3 months or older.[45] Crisaborole was developed with intentions of providing patients a topical treatment with an improved risk-benefit profile compared with that of TCSs and TCIs.[29] Most clinical experts prefer to start with TCSs and TCIs before trialing crisaborole.[18,35] PDE-4 degrades cAMP, which regulates cytokine synthesis.

Crisaborole leads to a small improvement in AD remission, itch, quality of life, and prevention of flares.[36] In turn, it has similar outcomes in comparison to low-potency TCS (group 6–7). Crisaborole can be used as an alternative to treatment for mild to moderate AD in patients who value non-corticosteroid treatments, or may be used as a steroid-sparing agent in sensitive areas. Although there are no limitations on its duration of use, crisaborole has not been well studied as proactive therapy.

Crisaborole 2% ointment is applied twice daily to the affected areas during flares. Common side effects include skin burning and stinging with application. Applying small quantities to a test area, particularly for sensitive areas of the body, may be helpful to evaluate the magnitude of adverse effects and its potential tolerability. Positive framing of potential sensations, precooling medication, and pretreatment with TCSs may reduce irritation.[18]

Topical JAK Inhibitors. Ruxolitinib is the only topical JAK1/2 inhibitor that is licensed in the United States as an alternative short-term treatment of mild to moderate AD in immunocompetent patients ages 12 years and above.[45] Topical delgocitinib is a pan-JAK inhibitor approved only in Japan for AD in adults.[18]

Short-term clinical studies have demonstrated that ruxolitinib 1.5% cream leads to improvement in AD severity, pruritus, sleep disturbances, and quality of life.[36,49] Topical ruxolitinib is slightly more potent in improving patient outcomes than pimecrolimus.[36] Although treatment is generally well tolerated with adverse effects consisting of local skin irritation, there is lack of long-term data regarding the safety and adverse events from potential systemic absorption. A boxed warning for serious infections, major cardiovascular events, thrombosis, malignancies, and all-cause mortality, reflecting the risk of patients taking JAK inhibitors orally (see Oral JAK Inhibitors below), was issued for topical ruxolitinib. Thus, expert consensus agrees against the use of topical ruxolitinib to avoid the uncertain small risk of serious harms over the modest benefits of treatment, especially when considering treatments with higher certainty for safety.[18]

Ruxolitinib 1.5% cream is applied as thin cream twice daily for up to 8 weeks or in a noncontinuous manner. It should be limited to less than 20% body surface areas to prevent toxicity in the setting of systemic absorption. The maximum dose is 60 g/wk or 100 g/2 wk. Its use should be avoided in patients who are immunocompromised or have risk factors that can contribute to adverse events.

Approach to Moderate to Severe Disease. Most patients with mild to moderate AD respond well to topical therapies alone. Additional therapy is required for patients with persistent signs and symptoms of AD despite an adequate trial of 2 to 4 weeks of a topical prescription therapy. Before therapy is advanced, the patient should be reassessed for nonadherence and have comorbid conditions treated.

For moderate to severe AD, adjuvant wet wrap therapy (WWT) and/or bleach baths are recommended to decrease AD severity and aid in disease control.[18] In WWT, wet dressings are used to occlude topical agents. This functions in decreasing transepidermal water loss, increasing percutaneous absorption of topical agents, soothing the skin, and providing a barrier from scratching. After bathing, topical agents are covered with moistened cotton clothing or gauze, followed by a dry second outer layer. Cotton mittens or tube socks can be used for the hands and feet. Wet wraps are placed for a minimum of 2 hours and may be left on overnight if needed. Once dry, the wraps are removed and a moisturizer is applied to the total body. WWT should be limited to 4 to 7 days to reduce the risk of skin maceration or infections.

For patients whose condition remains poorly controlled or is intolerant to topical therapy, step-up therapy is recommended in the form of phototherapy and/or systemic therapy. Recommended systemic therapies for the treatment for AD include injectable biologics, oral JAK inhibitors, and nontargeted immunosuppressive agents (e.g., cyclosporine)[18] (Table 1). Therapy choice should reflect a shared decision between the clinician and patient/caregiver. Considerations in treatment selection include drug efficacy, adverse risks, monitoring requirements, cost, convenience, access, and effect on the patient's quality of life. Topical therapy is typically continued in conjunction with systemic therapy.

Patients should be evaluated for improvement every 4 to 12 weeks. Once AD is controlled, the efficacy, safety, and need for systemic therapy should be reevaluated every 3 to 6 months. Discontinuing therapy may lead to rebound disease and patients should be aware of the potential need for lifelong treatment. There is a paucity of evidence regarding stopping AD medications, taking a temporary drug holiday, or reducing drug dosage after remission and should be considered on a case-by-case basis. Although new data may support the potential for tapering systemic therapies, topical therapy is typically continued indefinitely.

Biologics. Biologics have reshaped the treatment strategy for widespread, severe, or recalcitrant AD. Expert consensus recommends biologics as first-line systemic therapies for moderate to severe AD that is refractory or intolerant to topical medications.[18] Two biologics are approved for the treatment of moderate to severe AD in the United States: dupilumab and tralokinumab.[45] An NMA of 149 RCTs evaluating the benefits and harms of systemic AD therapies revealed that both dupilumab and tralokinumab led to improvements in multiple patient outcomes including AD severity, itch, sleep disturbances, and quality of life without an increase in serious adverse events or adverse events leading to treatment discontinuation.[50] Dupilumab has greater efficacy than tralokinumab and is generally preferred. Dupilumab is approved for adults and children 6 months and older. Tralokinumab is approved for ages 12 years or older.[45]

Dupilumab is a humanized monoclonal antibody that binds the IL-4 receptor alpha subunit (Figure). By blocking this subunit, it inhibits IL-4 and IL-13 signaling to reduce cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and IgE.[51] Tralokinumab is a humanized IgG4 monoclonal antibody that specifically binds to IL-13, thereby inhibiting its effect on production of inflammatory mediators and skin barrier disruption.[52]

Dupilumab and tralokinumab are administered as subcutaneous injections into the thigh, upper arm, or lower abdomen (avoiding areas within 2 inches of the navel.) Different injection sites should be selected with each use. Drugs should also not be administered in skin that is damaged, tender, bruised, or scarred. Patients may choose to self-administer after proper training or receive injections in-office. Strategies that may reduce pain or fear of injections include positive reframing, visual or auditory distractions, breathing techniques, icing the injection site or using a local anesthetic, and small vibration or cooling devices.[18]

Dupilumab dosing interval varies by age and is administered every 2 to 4 weeks[18,45] (Table 1). In patients aged 18 years or older, a loading dose of 600 mg (given as two 300-mg injections at separate sites) is administered and followed by maintenance dosing of 300 mg every other week. In patients aged 6 months to 17 years, dose is adjusted for weight. A loading dose is not necessary for patients younger than 6 years. Instead, a 200-mg (<15 kg) or 300-mg dose (15 to <30 kg) is administered every 4 weeks. In patients 6 to 17 years of age, an initial loading dose is given (15 to <30 kg: 600 mg; 30 to <60 kg: 400 mg; ≥60 kg: 600 mg) followed by a maintenance dose (15 to <30 kg: 300 mg every 4 weeks; 30 to 60 kg: 200 mg every other week; ≥60 kg: 300 mg every other week). Tralokinumab dosing is age dependent only (Table 1). In patients 12 to 17 years of age, an initial 300-mg dose is administered followed by a maintenance dose of 150 mg every other week. In adult patients, tralokinumab is given as a loading dose of 600 mg followed by 300 mg every other week. For both biologics, there are no dosage adjustments provided for kidney and/or liver impairment. There is no routine laboratory monitoring required before and during use.

Maximum therapeutic benefit for dupilumab and tralokinumab occurs at week 16 although some may continue to have improvement for a year.[18] Full-dose recommendations should be continued until AD is adequately controlled. If remission is sustained for at least 6 months, the dosing frequency can be extended.[53] However, dosing intervals greater than 4 weeks tend to lead to inferior control than more frequent dosing. If AD worsens with dose adjustment, the previous frequency used to achieve remission should be reinstated.

The biologics used in AD have an excellent safety profile in clinical trials across all ages and have few emergent safety concerns.[18,50,54,55] The most frequent adverse effects are ocular surface disease and injection-site reactions. Ocular surface complications, most commonly conjunctivitis, are typically mild and self-limiting, but can be treated with warm compresses, lubricant eye drops, ophthalmic corticosteroids and/or antihistamines, and mast cell stabilizers. Risk factors for the development of dupilumab-associated conjunctivitis include AD severity and history of prior conjunctivitis. Severe ocular symptoms such as decreased visual acuity, diplopia, eye pain, photophobia, and purulent eye discharge require urgent ophthalmology referral. Peripheral eosinophilia is common with dupilumab, but tends to resolve by week 16. Although herpes viral infection rates are higher with dupilumab than with placebo, the risk of serious infection rates tend to be reduced.[18] Face and neck erythema was not reported in phase 3 clinical trials, but a number of cases have been reported in the real world.[54] Its etiology is unknown and the most frequently used treatments were TCSs, TCIs, and topical antifungals with varied results.[55] There have also been reports of inflammatory arthritis and psoriasiform eruptions. Concomitant treatment of these adverse events allows for continuation of treatment. Limited data are available regarding vaccination administration during biologic use for AD. Moreover, concomitant use of non–live vaccines appears safe and efficacious. Live vaccine administration is recommended to be completed before initiating biologics, if possible.

Oral JAK Inhibitors. The JAK-STAT signaling pathways are responsible for the production of many cytokines and growth factors and have a vital role in many chronic inflammatory disorders. Given their ability to suppress many immune pathways, they were originally approved for the use in various autoimmune disorders. More recently, oral JAK inhibitors have been licensed as second-line treatments of moderate to severe AD when the disease is not controlled by other systemic therapies (including biologics) or when other therapies are inadvisable.[45] Two agents are FDA (US Food and Drug Administration) approved: abrocitinib, for ages 18 years or older, and upadacitinib, for ages 12 years or above. Baricitinib is approved by the European Medical Agency for AD in adults, but not in the United States.[18]

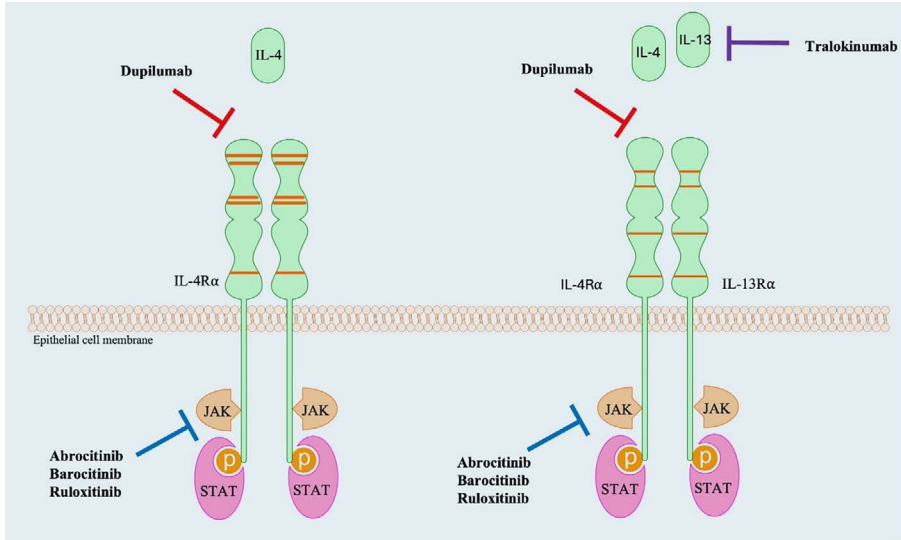
JAK inhibitors are among the most effective systemic therapies for AD but are the most harmful.[50] The efficacy varies by drug and is dose dependent. Upadacitinib exhibits the highest efficacy (30 mg > 15 mg), followed by abrocitinib (200 mg >100 mg), then baricitinib (4 mg > 2 mg). Compared with dupilumab, upadacitinib is superior in efficacy for multiple important patient outcomes including early improvement in itch and skin clearance.[50] Abrocitinib is likely similar in efficacy to dupilumab. All oral JAK inhibitors may initially lead to faster clinical response rates than dupilumab.[56] This effect may be advantageous in certain situations. For example, oral JAK inhibitors may allow for acute control of severe AD before a major life event or while bridging to safer therapies.[18]

JAK1 is an important receptor signal transducer for many of the cytokines involved in the inflammation of AD, including IL-4, IL-5, IL-13, and IL-31. Abrocitinib and upadacitinib are selective JAK1 inhibitors. Baricitinib is a nonselective JAK1/JAK2 inhibitor (Figure).

Abrocitinib 100 mg once daily or upadacitinib 15 mg once daily are the recommended starting doses.[18,45] However, dose adjustments are required for renal impairment and patients receiving cytochrome P450 inhibitors. Furthermore, the use of oral JAK inhibitors has not been studied in end-stage hepatic or renal disease and is not recommended in these groups. Clinical benefits may be seen within days of starting therapy, while maximum improvement occurs by week 16. If there is an inadequate response at 3 months, the dose may be increased to abrocitinib 200 mg once daily or upadacitinib 30 mg once daily. Following AD clearance, the lowest possible dose should be used for maintenance.

Although associated with more adverse effects than other therapies for AD, clinical studies have

Figure. Mechanism and blocking effects of dupilumab on the IL-4 receptor and preventing the binding of both IL-4 and IL-13. The figure also shows the mechanism and inhibitory effects of abrocitinib, barocitinib, and ruloxitinib on JAK.



IL, interleukin; JAK, Janus kinase.

demonstrated that oral JAK inhibitors are usually well tolerated compared with placebo controls.[57,58] The most common adverse events (>5% of patients) of oral JAK inhibitors include nausea, headache, and acne. The acne is usually mild and can be managed with conventional topical therapies (e.g., topical retinoid). Upadacitinib is associated with an increased rate of upper respiratory infections and nasopharyngitis, and less commonly, herpetic infections. Other notable side effects are laboratory abnormalities including an elevated creatinine phosphokinase concentration, and dose-dependent changes in lipid profile and platelets with abrocitinib. An FDA black box warning was recently placed on all JAK inhibitors regarding increased risk of major adverse cardiovascular events, venous thromboembolism, serious infections, malignant neoplasm, and death, based on safety data from a trial with oral tofacitinib in rheumatoid arthritis.[18,45,57] However, the rate of these serious adverse events are low in AD and likely reflect additional risk-specific factors to the event.[57] In a recent systematic review and NMA, use of JAK inhibitors was not associated with increased risk of all-cause mortality, major adverse cardiovascular events, and venous thromboembolism when compared with the placebo/active comparator groups.[59] However, there is a paucity of data on the long-term safety of oral JAK inhibitors in AD.

Before starting therapy with JAK inhibitors, a comprehensive evaluation of a patient's baseline risk factors and comorbid conditions is critical to prevent serious harm.[18,57] Patients who are poor candidates and at increased risk of adverse events include elderly persons; persons with significant cardiovascular history, history of venous thrombosis, or active cancer; or persons who are immunocompromised. Baseline peripheral blood cell counts as well as renal and liver function panels should be established, monitored after 1 month, and every 3 months thereafter. Baseline lipid profile is screened before therapy and monitored after 3 months. Patients should be screened for serious infections including tuberculosis (TB), viral hepatitides, and HIV. Annual TB screening is recommended during long-term therapy. Patients should have all age-appropriate cancer screenings and vaccinations up-to-date. It is recommended that patients receive pneumococcal and Shingrix (inactivated, adjuvanted, subunit vaccine, GlaxoSmithKline, Middlesex, United Kingdom) vaccines before starting therapy. JAK inhibitors should not be used in combination with other potent immunosuppressive agents, and the use of antiplatelets (other than 81-mg aspirin) is prohibited in the first 3 months of therapy. Dose reduction or pausing may be required if cytopenias (platelet count <150,000/mm^3, absolute lymphocyte count <500/mm^3, absolute neutrophil count <1000/mm^3, or hemoglobin <8 g/dL) or infections develop during therapy.

Nontargeted Immunosuppressives: Cyclosporine. Conventional immunosuppressives were commonly used off label for severe AD control in all ages. More recently, they are now used as second-line therapies for patients with moderate to severe AD that is

refractory, intolerant, or unable to use topical and systemic therapy inclusive with a biologic.[18] These agents include cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and corticosteroids. However, expert consensus recommends only the use of cyclosporine in the treatment paradigm of AD.[18]

Cyclosporine inhibits production and release of IL-2, thereby inhibiting IL-2–induced activation of T cells. It has demonstrated efficacy in treating AD in children and adults.[60,61] Cyclosporine is used for short-term control of flares refractory to first-line therapies and as a bridge to alternative systemic therapies. Low-dose cyclosporine has been shown to be non-inferior to high dose.[62] Thus, the recommended starting dose is 2.5 to 3.5 mg/kg/day in 2 divided doses for up to 16 weeks.[63] Once remission is achieved, the dose should be lowered to the minimal effective dose (0.5–1 mg/kg/day) every 2 weeks. To prevent rebound AD, cyclosporine should be tapered before discontinuation. Its use should be limited to 1 to 2 years to prevent associated adverse events, which most commonly include nephrotoxicity and hypertension. Routine laboratory values (complete blood count, renal and liver function studies) and blood pressure should be monitored biweekly for the first 1 to 2 months, then every 1 to 3 months with continued therapy. During infections, therapy may need to be reduced or paused.

Phototherapy. Narrowband ultraviolet B (NBUVB) is effective at reducing AD severity and pruritus when compared with placebo.[50,64] Expert consensus recommends the use of NBUVB in patients with moderate to severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic.[18,65] Phototherapy may be advantageous in patients who prefer treatments with minimal adverse effects, who do not require drug monitoring, or when other second-line therapies fail or are inadvisable. In addition, NBUVB may be a safe alternative in patients of child-bearing age. However, phototherapy use is limited owing to availability and time constraints. Poor candidates for phototherapy include patients with photodermatoses or those with an increased risk for skin cancer.

NBUVB consists of 311- to 313-nm-wavelength light delivered by targeted devices or specialized cabinets. The treatment duration and frequency of NBUVB depend on the patient's skin type and response to therapy. Patients typically require 3 sessions per week for 5 to 30 minutes. Phototherapy is typically well tolerated. Adverse effects include skin burning, irradiation, tanning, and reactivation of herpes infection.[64] Premature skin aging and skin cancer are less likely to occur with NBUVB than with other UV phototherapies.

Adjuvant Therapies. Allergen immunotherapy (AIT) involves the gradual exposure of an allergic patient to an allergen in order to build a tolerance to it. It is a treatment option for patients who have proven sensitization to an allergen and disease exacerbation upon exposure. Allergen immunotherapy may be administered sublingually or subcutaneously. A recent systematic review of 23 RCTs demonstrated that patients with add-on AIT were more likely to achieve a 50% reduction in AD severity and improvement in quality of life than no AIT use.[66] Expert consensus thus recommends AIT in patients with moderate to severe AD uncontrolled with standard topical medications alone, especially if there is comorbid allergic disease.[18]

Elimination diets are commonly used by patients to improve signs and symptoms of AD. A systematic review of 10 RCTs comparing dietary restriction with no dietary restriction demonstrated a slight, but unimportant improvement in AD severity, sleep, and itch in patients with mild to moderate AD.[67] However, this improvement is outweighed owing to the risk of malnutrition and growth restriction. Food avoidance is also strongly associated with development of IgE-specific food allergies. Therefore, it is recommended that elimination diets be avoided because the potential for little to no benefit does not outweigh the risk of serious harms.[18]

The Airplane View of an Experienced Clinician

The evaluation and treatment of an infant with AD depends on the history collected. Is itching a component trigger? Resolution of the itch with an antihistamine at bed may help resolve the skin inflammation. When did the dermatitis show up? Early onset may be related to milk. As food is introduced more food triggers may be the culprit. If breastfeeding is chosen by the parent, then any food that the mother is eating may be to blame for skin exacerbations. Eggs are a very common provocateur. Does the skin have yellow honey-colored crust on the skin? *Staphylococcus aureus* infection of the skin may trigger a total body worsening. Treatment of the infection may resolve the inflammatory response. Does the parent use a fragrant moisturizer for the infant? Fragrance items may complicate AD as an overlying contact dermatitis. Is the infant's skin excessively dry? Continual hydrating of the skin will often result in improvement and possibly resolution of AD. Topical steroids of various strength as well as calcineurin inhibitors may be used for AD. Once the skin improves to a satisfactory state, the steroids may be weaned off but may be reapplied for exacerbations. As the infant progresses in age, the AD may resolve but leave with the onset of asthma in the allergic march. With the improvement of the skin with age the therapeutic options described may be weaned off and used as needed. Food allergies like egg and milk may resolve and stop becoming a trigger for AD. The adult patient with AD may be treated similarly with less reliance on food as a trigger. More severe cases in pediatric patients and adults that do not resolve or improve with

the above therapies may require biological or JAK inhibitor intervention. These products do work very well. Unfortunately, there is no exit strategy for their use. Their use may be for a lifetime. The treatment of AD has progressed, and the future looks brighter for our affected patients.

Conclusion

Atopic dermatitis is a lifelong inflammatory skin disease burdening the quality of life of millions of children and adults globally. The effects are not limited to the intense pruritus that characterizes eczematous lesions but are associated with risks of other systemic disease including progression to other allergic comorbidities. The systemic nature of the disease illustrates the importance of creating individualized treatment plans to combat multifaceted, although still not understood, pathophysiology. Further research into the pathogenesis and subtypes of AD will continue to allow more targeted therapies in the future.

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