

CME Review

Atopic dermatitis

Review of comorbidities and therapeutics



Margaret M. Appiah, BS^{*,†}; Michael A. Haft, BS^{*,†,‡}; Elana Kleinman, BS[†]; Jennifer Laborada, BS[†]; Stephanie Lee, MD^{*,†}; Lauren Loop, BS[†]; Bob Geng, MD^{†,§}; Lawrence F. Eichenfield, MD^{*,†}

^{*} Departments of Dermatology and Pediatrics, University of California San Diego, San Diego, California

[†] Rady Children's Hospital, San Diego, California

[‡] University of Rochester School of Medicine, New York, New York

[§] Division of Allergy and Immunology, University of California San Diego, San Diego, California

Key Messages

- Atopic dermatitis follows a variable disease course throughout a patient's life.
- Atopic dermatitis is associated with cardiovascular disease and allergic conditions.
- Novel biologics and oral Janus kinase inhibitors are efficacious options for patients with moderate-to-severe disease.
- Janus kinase inhibitors are especially rapid in their itch control.

ARTICLE INFO

Article history:

Received for publication April 8, 2022.

Received in revised form May 8, 2022.

Accepted for publication May 12, 2022.

ABSTRACT

Atopic dermatitis (AD) is a very common skin disease associated with substantial burdens on patient health and quality of life. Knowledge regarding the pathogenesis of AD has expanded within recent years, leading to novel and efficacious therapeutic agents. Similarly, our knowledge of the impact of AD on patient's mental and physical health has also expanded. This review summarizes updates on the evolution, comorbidities, and therapeutic options of AD.

AD is associated with increased cardiovascular risk, allergic diseases, and adverse mental health outcomes. Topical and systemic therapeutics have drastically altered the landscape of AD therapy in recent years.

© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc.

Introduction

Atopic dermatitis (AD) is an extremely common skin disease, affecting up to 25% of children and 7% of adults.¹ The pathogenesis of AD is multifactorial and includes skin barrier dysfunction, inflammation, dysbiosis, and modulation by genetic and environmental factors. Patients generally present with xerosis, erythema, induration, excoriations, lichenification and pruritus.¹ AD is associated with quality-of-life impact for both patients and family members, and patients with AD are at higher risk for a set of allergic and nonallergic comorbidities. In addition to traditional topical and systemic therapies, there are now

additional novel topical and systemic medications available and in later-phase clinical studies which are changing the landscape of AD therapy. This article emphasizes important points of consideration for AD management and reviews emerging therapeutics.

Onset, Comorbidities, and Quality-of-Life Impact

Onset and Disease Course

AD presents most often in childhood, with traditional teaching stressing that most patients with AD develop disease within the first year of life.¹ However, the variability among patients in terms of disease onset and course is now better understood. In addition, a small subset of patients may develop AD in adulthood.² A 2018 longitudinal study by Paternoster et al³ evaluated 2 cohorts of patients with AD from birth to 11 to 16 years of age; this study found 6 distinct "subgroups" of onset and persistence of AD, including "unaffected/transient," "early-onset-early-resolving," "early-onset-late-resolving," "mid-onset-resolving," "late-

Reprints: Lawrence F. Eichenfield, MD, Rady Children's Hospital, 3030 Children's Way, MC5092, San Diego, CA 92123. E-mail: leichenfield@rchsd.org.

Disclosures: Dr Geng has served as advisor, consultant, speaker, investigator for: Abbvie, Pfizer, Sanofi, Regeneron, Galderma, Genentech, Novartis. Dr Eichenfield has served as a scientific adviser, consultant, and/or clinical study investigator for AbbVie, Almirall, Arcutis, Arena, Aslan, Dermavant, Eli Lilly, Forté, Galderma, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron and Sanofi, Genzyme.

Funding: The authors have no funding sources to report.

<https://doi.org/10.1016/j.anai.2022.05.015>

1081-1206/© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc.

Instructions

Credit can now be obtained, free for a limited time, by reading the review article and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test.
- Read the article and reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned. At this time, physicians will have earned up to 1.0 AMA PRA Category 1 Credit™. Minimum passing score on the post-test is 70%.

Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

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

- Describe the common comorbidities of atopic dermatitis.
- Discuss the mechanisms of action and common side effects of novel therapeutic agents.

Release Date: August 1, 2022

Expiration Date: July 31, 2024

Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology.

Accreditation

The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation

The American College of Allergy, Asthma & Immunology (ACAAI) designates this journal-based CME activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Statement

As required by the Accreditation Council for Continuing Medical Education (ACCME) and in accordance with the American College of Allergy, Asthma and Immunology (ACAAI) policy, all individuals in a position to control or influence the content of an activity must disclose all financial relationships with any ineligible company that have occurred within the past **24 months**. The ACCME defines a “ineligible company” as companies whose primary business is producing, marketing, re-selling, or distributing health care goods or services, used by or on patients. Examples of such organizations include:

- Bio-medical startups that have begun a governmental regulatory approval process
- Compounding pharmacies that manufacture proprietary compounds
- Device manufacturers or distributors
- Diagnostic labs that sell proprietary products
- Growers, distributors, manufacturers or sellers of medical foods and dietary supplements
- Manufacturers of health-related wearable products
- Pharmaceutical companies or distributors
- Pharmacy benefit managers
- Reagent manufacturers or sellers

The ACCME does not consider providers of clinical service directly to patients to be commercial interests. For more information, visit www.accme.org. All identified relevant relationships must be mitigated and the educational content thoroughly vetted for fair balance, scientific objectivity, and appropriateness of patient care recommendations. It is required that disclosure of or absence of relevant financial relationships be provided to the learners prior to the start of the activity.

Learners must also be informed when off-label, experimental/investigational uses of drugs or devices are discussed in an educational activity or included in related materials.

Disclosure in no way implies that the information presented is biased or of lesser quality. It is incumbent upon course participants to be aware of these factors in interpreting the program contents and evaluating recommendations. Moreover, expressed views do not necessarily reflect the opinions of the ACAAI. **All identified relevant financial relationships have been mitigated.**

Planner

- John Oppenheimer, Advisor, Amgen, Aquestive; Independent Contractor/Adjudication AstraZeneca, Novartis; Advisor/Independent Contractor/DSMB GlaxoSmithKline; Independent Contractor, Sanofi; Independent Contractor, Regeneron.

Authors:

- Margaret Appiah, BS, has no relevant financial relationships with ineligible companies to disclose.
- Michael A. Haft, BS, has no relevant financial relationships with ineligible companies to disclose.
- Elana Kleinman, BS, has no relevant financial relationships with ineligible companies to disclose.
- Jennifer Laborada, BS, has no relevant financial relationships with ineligible companies to disclose.
- Stephanie Lee, MD, has no relevant financial relationships with ineligible companies to disclose.
- Lauren Loop, BS, has no relevant financial relationships with ineligible companies to disclose.
- Bob Geng, MD, Advisor/Consultant/Speaker: Pfizer, Regeneron, Sanofi; Advisor: ADMA, Galderma, Koru; Contracted Research: AstraZeneca, Novartis; Speaker: GlaxoSmithKline, OptiNose, Teva; Speaker/Advisor: BioCryst, Chiesi, Grifols, Horizon, Takeda.

- Lawrence Eichenfield, MD, Consultant: Amgen, Arena, Lilly, Otsuka; Consultant/Investigator: Abbvie, Dermavant, Galderma; Consultant/Advisory Board: Asian; Consultant/Advisory Board/Investigator: Arcutis; Speaker/Consultant/Advisory Board: LEO, Regeneron, Sanofi; Speaker/Consultant/Advisory Board/Investigator: Incyte, Pfizer; Board of Directors/Stockholder: Forte.

Recognition of Commercial Support: This activity has not received external commercial support.

Copyright Statement: © 2015–2022 ACAAI. All rights reserved.

CME Inquiries: Contact the American College of Allergy, Asthma & Immunology at education@acaai.org or 847-427-1200.

onset-resolving,” and “early-onset-persistent.” A 2016 meta-analysis found that AD persistence varied based on the age of disease onset, with earlier-onset disease being less persistent than later-onset disease.⁴ Later childhood- and adult-onset AD is now appreciated as not uncommon. These data suggest the heterogeneous nature of this disease.

Allergic Comorbidities

The association between AD and other allergic conditions is well established. Adults with AD are 3 times more likely than the general population to have asthma,⁵ and the relative risk of asthma increases with the severity of AD; compared with patients without AD, patients with severe AD have a relative risk (RR) of asthma of 2.38 (confidence interval [CI], 1.91–2.85) vs an RR of 1.34 (1.12–1.56) for patients with mild AD.⁵ Adult patients with AD may also have higher rates of allergic rhinitis than non-AD individuals, although there are relatively few studies evaluating this relationship and there is variability in the magnitude of association in the available studies.⁵ In a cross-sectional study of more than 2200 children, nearly 80% had some form of allergy (asthma, allergic rhinitis, animal allergy, food allergies, drug allergies),⁶ with 38% having asthma and allergic rhinitis.

The clinical implications of food allergies in AD remain unclear. Although there is an association between AD and presence of food allergy in adults, these data are limited by heterogeneity in the definition and identification of food allergies in available studies.⁵ However, there is evidence of a positive relationship between severity of AD and odds of food allergy; compared with the general population, the risk is higher in severe AD (RR, 8.49; 95% CI, 5.44–11.54) than moderate (RR, 2.40; 95% CI, 1.54–3.27) or mild (RR, 1.48; 95% CI, 0.89–2.07) AD.⁷

In children, the relationship between AD and food allergies is more extensively studied. Data reveal a link between AD and food allergy prevalence.^{8–10} Interestingly, there have been multiple recent studies revealing that elimination diets in pediatric patients with AD may actually increase immediate symptoms of food allergies. In patients with AD, reintroduction of eliminated foods may lead to immediate food allergy symptoms in 13% to 20% of patients,^{11–13} with up to 30% of these children developing anaphylaxis on re-exposure.¹² It is hypothesized that aggressive, early treatment of AD in infancy may in fact reduce the risk of food allergy development.¹⁴ The question “What role might food allergy tests play in treating eczema?” has been identified as a top 10 priority research question for AD.¹⁵

Mental Health

AD is associated with negative mental health outcomes, including depression, anxiety, and suicidal thoughts.^{16,17} In a longitudinal cohort study of 11,181 children from the United Kingdom, investigators found that subjectively severe AD was associated with an increased risk of depression and anxiety (adjusted odds ratio [OR], 5.18; 95% CI, 2.06–13.04).¹⁷ Worsening AD severity was also associated with increased odds of experiencing depressive symptoms. Those with active AD had increased odds of exhibiting internalizing behaviors (adjusted OR, 1.41; 95% CI, 1.17–1.70) and increasing AD

severity had a dose-dependent effect on odds of such behaviors.¹⁸ Adults with AD carried almost double the odds of depression (OR, 1.99; 95% CI, 1.53–2.59), 40% increased odds of anxiety (OR, 1.40; 95% CI, 1.12–1.75), and 71% increased odds of suicidal ideation (OR, 1.71; 95% CI, 1.43–2.03) compared with nonaffected counterparts.⁵ The National Survey of Children’s Health found significant associations between pediatric AD and autism, conduct disorders, attention deficit hyperactivity disorder, and depression and anxiety, with odds ratios of 3.04 (95% CI 2.13, 4.34), 1.87 (1.46, 2.39), 1.87 (95% CI 1.54, 2.27), 1.81 (95% CI 1.33, 2.46), and 1.77 (95% CI 1.36, 2.29).¹⁹

Family Impact

The quality-of-life effects of AD can also extend to patient’s family members. In a 2005 study of 270 patients with AD, 61% of parents reported that their own sleep was disturbed by their child’s AD, with parental sleep disturbance associated with their child’s disease severity ($P < .001$).²⁰ In an investigation of 55 children with moderate-to-severe AD or asthma by Moore et al²¹, mothers and fathers spent a median of 78 and 90 minutes per night respectively dealing with their child vs 0 minutes for parents of children with asthma.²¹ Increased sleep disturbances correlated with increased odds of anxiety (OR, 4.6; 95% CI, 1.6–13; $P = .005$) and depression (OR, 7.9; 95% CI, 2.8–23; $P = .001$) in mothers and increased odds of anxiety (OR, 4.9; 95% CI, 1.6–15; $P = .006$) in fathers caring for children with AD compared with parents caring for children with asthma.²¹ Yang et al²¹ found that multiple studies revealed harmful effects to the marital relationship of the parents of an affected child, including blaming partners for the affected child’s disease, decrease in socializing outside the home, and decreased intimacy.²² This evidence reveals that AD affects not only patients but also the physical, mental, and psychosocial health of caregivers.

Cardiovascular Comorbidities

AD has been associated with cardiovascular (CV) disease⁵ with assessment that hypertension and coronary artery disease are “probably associated” with AD.⁵ Comorbid risk factors cited are obesity, smoking, and heavy alcohol consumption, including elevated atherosclerosis-associated proteins.^{23–26} In a UK cohort study of more than 380,000 individuals with AD, severe disease burden correlated with increased risk of atrial fibrillation (hazard ratio [HR], 1.35; 95% CI, 1.14–1.59), unstable angina (HR, 1.4; 95% CI, 1.02–1.95), myocardial infarction (HR, 1.37; 95% CI, 1.12–1.68), and CV death (HR, 1.30; 95% CI, 1.10–1.53).²⁷ A dose-response relationship was also observed between AD severity and risk of congestive heart failure (mild AD; HR, 1.12; 95% CI, 1.02–1.24) (severe AD; HR, 1.67; 95% CI, 1.36–2.05).²⁷ A systematic review and meta-analysis of population-based studies of patients with AD found that increasing AD severity was associated with higher risk of angina (RR per-unit increase in severity 1.16, 95% credibility interval [CrI]; analogous to 95% CI for the mean), 1.07–1.27), myocardial infarction (RR, 1.14; 95% CrI, 1.05–1.23), heart failure (RR, 1.20; 95% CrI, 1.06–1.36), and CV death (RR, 1.25; 95% CrI, 1.13–1.38).²⁸ The mechanism behind these correlations is unclear.

	MILD	MODERATE	SEVERE	Considerations • Nonadherence • Infection • Misdiagnosis • Contact allergy
Acute	Apply TCS to Inflamed Skin Low-to-medium potency TCS, twice daily for 2 wks → daily x 1wk, few days beyond clearance Alternative: Consider crisaborole 2% or TCI or ruxolitinib 1.5%	Apply TCS to Inflamed Skin Medium-to-high potency TCS, twice daily for 2 wks → daily x 1wk → twice per week to “hot spots,” few days beyond clearance For sensitive areas: Low potency TCS or consider Crisaborole 2% or TCI Alternative: Consider crisaborole 2% or TCI or Ruxolitinib 1.5%	Apply TCS to Inflamed Skin Medium-to-high potency TCS, twice daily for 2 wks → daily x 1wk → twice per week to “hot spots”; 3-7 days beyond clearance For sensitive areas : Lower potency or consider Crisaborole 2% or TCI if unresolved after 7 d, reconsider plan	
Maintenance	(Basic management) 1. Skin Care Liberal, frequent moisturizer use Daily warm bath/shower, followed by moisturizer 2. Trigger Avoidance Common irritants; allergens if proven Consider comorbidities	(Basic management +) Maintenance TCS or – Medium potency, 2-3 times weekly (“proactive”) to recurrently active areas of involvement – Low potency TCS several times weekly for sensitive areas Maintenance TCI, twice daily OR – 2-3 times weekly (proactive approach)^a Crisaborole 2%, twice daily OR – Several times weekly^a Ruxolitinib 1.5%, twice daily – Several times weekly^a Consider: Adding Bleach Baths – 2-7 times weekly based on severity and tendency to develop crusting at sites of excoriation	(Basic + Moderate management + REFERRAL to AD Specialist) Phototherapy Dupilumab Abrocitinib Upadacitinib Systemic Immunosuppressants – Cyclosporine A – Methotrexate – Mycophenolate mofetil – Azathioprine – Corticosteroids Consider acute treatment for some patients to help gain control – Wet wrap therapy – Short-term hospitalization	
Advance: when symptomatic despite appropriate use of medications and adherence to management and/or frequent flaring				

Figure 1. A treatment algorithm for initial and step-up management of patients with AD based on severity. Adapted from Boguniewicz M, et al. *Ann Allergy Asthma Immunol*. 2018;120(1):10-22. ^aNo specific FDA approval of intermittent dosing of Pimecrolimus, Tacrolimus, and Crisaborole. Note: Several medications have specific age indications. AD, atopic dermatitis; FDA, Food and Drug Administration; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

AD may cause considerable stress resulting in maladaptive behaviors leading to the development of other CV risk factors. However, given AD's independent association with systemic inflammation, the disease on its own may be an independent risk factor for poor CV outcomes.

Nontherapeutic Management

Skin Care

A key component of AD pathophysiology is epidermal barrier dysfunction, increased transepidermal water loss, and clinical xerosis. Hence, moisturization is considered a cornerstone of AD management. Strong evidence exists for topical moisturizers as an important aspect of AD care.² Application of moisturizers increases skin hydration, reduces AD signs and symptoms such as pruritus and erythema, and can decrease the amount of prescription anti-inflammatory treatments needed.²⁹ A 2017 systematic review of randomized

controlled trials assessed the effect of moisturizer use for AD. A total of 77 studies with 6603 participants were included in their analysis. Investigators found that, compared with no treatment, moisturizers reduced the number of participants who experienced a flare (RR, 0.39; 95% CI, 0.22-0.68; $P = .001$), changed participants' SCORing Atopic Dermatitis score by a mean of -2.51 (95% CI, -3.66 to -1.37 ; $P < .001$), and decreased the amount of topical steroids used over the course of 6 to 8 weeks ($P < .001$). In addition, they found that moisturizer use reduced the rate of AD flare and prolonged the time to flare.³⁰

Bathing

There is currently no standard for best bathing practices for patients with AD, particularly in regard to frequency and duration. Bathing helps reduce scale, crust, allergens, and irritants and may decrease cutaneous bacteria colonization. It is recommended to use nonsoap cleansers that are neutral to low pH and hypoallergenic.³¹

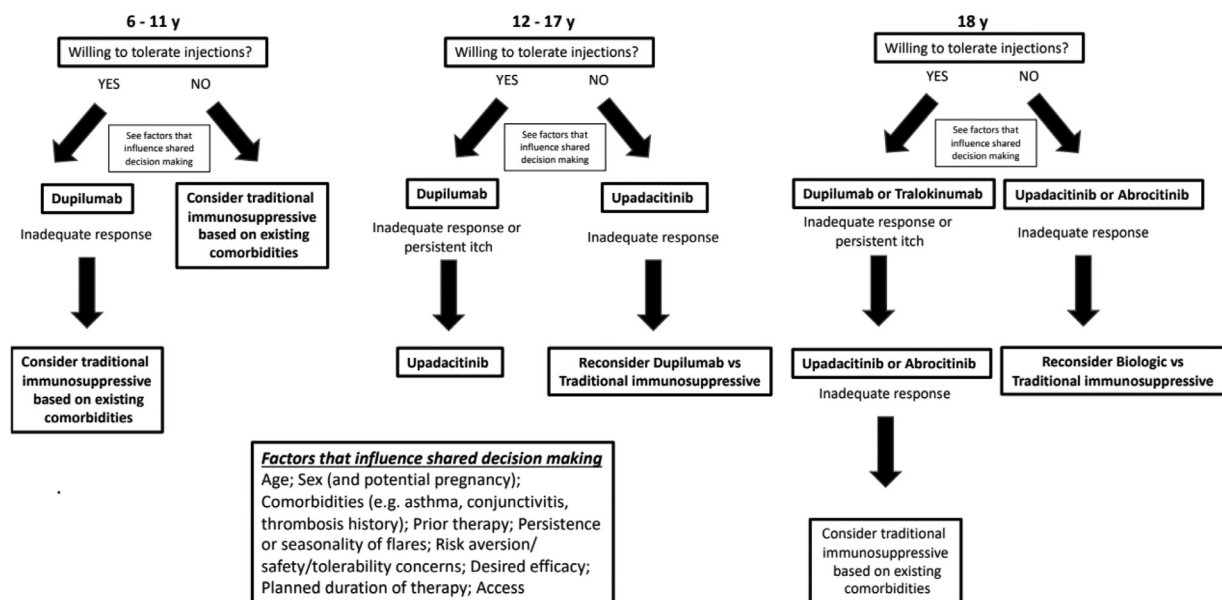


Figure 2. A proposed decision tree for deciding between systemic therapies for patients who have failed topicals.

Bathing without the application of an emollient afterward may compromise skin hydration and exacerbate xerosis.³¹ Standard guidelines for management of AD do not give a recommendation for bathing duration and frequency given the lack of evidence to support any 1 bathing regimen.²⁹

Topical Therapies

Topical Corticosteroids

For patients who have inadequate control with topical emollients alone, first-line therapy is topical corticosteroids (TCSs).³² These medications have been studied for more than 60 years, and their efficacy has been found in many randomized controlled trials.²⁹ Treatment of actively inflamed skin generally involves twice-daily application of TCS to active disease areas, though once-daily application may be sufficient depending on agent used and clinical circumstance. Intermittent use of TCSs (2–3 times per week) may also be used as maintenance therapy to help prevent flares.²⁹ Extensive and long-term TCS use in certain areas of the body may cause localized skin atrophy, telangiectasia, striae, perioral dermatitis, and acne.³³ In addition, there is a very low but present risk of hypothalamic-pituitary-adrenal axis suppression with the use of TCSs, especially with the long-term use of higher potency agents.²⁹ Historically, patients and caregivers often underuse TCSs because of fear of adverse effects, also known as “steroid phobia.”²⁹ Recognition of patient concerns and appropriate counseling regarding the safety profile of TCSs and suggestions of appropriate volumes of TCS to use over time may improve adherence and increase disease control.²⁹

Nonsteroidal Topical Agents

Nonsteroidal topical alternatives include topical calcineurin inhibitors (TCIs), tacrolimus and pimecrolimus. This class of anti-inflammatory therapy was first introduced in the early 2000s and is considered second-line topical therapy for patients with AD.²⁹ Tacrolimus 0.03% and 0.1% ointments are approved for adults and 0.03% for children aged 2 to 15 years with moderate-to-severe AD.³⁴ Pimecrolimus 1% cream is indicated for non-immunocompromised adults and children aged more than or equal to 2 years with mild-to-moderate AD.³⁵ TCIs are recommended as steroid-sparing agents for use on affected areas, but may cause skin burning and pruritus in some patients, especially when applied to actively inflamed skin. Patients with AD should be counseled about the possibility of these reactions and should consider treatment with TCSs when initiating TCIs to minimize application site reactions.²⁹

More recently, topical phosphodiesterase-4 (PDE4) inhibitors, such as crisaborole 2% ointment, received approval from the Food and Drug Administration (FDA) for adults and children aged more than 3 months with mild-to-moderate AD.^{36,37} By inhibiting PDE4, an intracellular enzyme that regulates inflammation and epithelial integrity, this class of therapeutics is able to play a role in decreasing the skin inflammation and pruritus associated with AD. A major adverse effect of this class is burning and stinging.^{36,37} Other topical phosphodiesterase inhibitors are currently under investigation. One particular PDE4 inhibitor, roflumilast, has completed phase III studies for plaque psoriasis and is currently in phase III clinical trials for treating mild-to-moderate AD in patients as young as 2 years old (Clinicaltrials.gov identifiers NCT04773600, NCT04845620).

Janus kinase inhibitors (JAKis) are the newest class of topical therapeutics for AD. Given recent efforts to further understand the pathogenesis of AD, it was identified that the JAK-STAT signaling pathway plays an influential role in the pathogenesis of AD through several key cytokines. Recently, topical Ruxolitinib cream, a topical inhibitor of JAK 1 and JAK 2, was the first topical JAKi to gain FDA approval for short-term and noncontinuous long-term treatment of mild-to-

moderate AD in non-immunocompromised patients aged more than or equal to 12 years.³⁵ Of note, pharmacokinetic data studying maximal use of topical ruxolitinib revealed that serum levels in some individuals with extensive eczema body surface area involvement approached levels similar to that of low-dose oral ruxolitinib. However, studies with the approved topical 1.5% ointment used in patients with up to 20% body surface area involvement did not reveal evidence of accumulation or hematologic changes of clinical significance over time.³⁸

Tapinarof is a new topical therapy under investigation with a novel mechanism of action in treating AD; it activates the aryl hydrocarbon receptor which inhibits the interleukin IL-4 and IL-13-mediated STAT6 pathway and increases expression of filaggrin, loricrin, and involucrin.³⁹ It was originally derived as a small molecule produced by bacterial symbionts.⁴⁰ Tapinarof is in late stages of clinical trials for both psoriasis and AD and has reached phase III trials for adults and children more than 2 years old with moderate-to-severe AD (Clinicaltrials.gov identifier NCT05014568).

Microbiome Therapies

Another potential avenue of therapy is modulating the skin microbiome in attempts to modulate AD. One such candidate was the commensal gram-negative bacteria *Roseomonas mucosa* applied as a topical live biotherapeutic agent. Despite initial promising results, a phase II study in 154 subjects failed to meet primary end points compared with placebo.⁴¹ Another candidate under investigation is *Staphylococcus hominis* (ShA9), a skin commensal that selectively inhibits nonresident pathogenic bacteria. A phase I and II trial in 54 subjects with moderate-to-severe AD revealed that topical application of ShA9 decreased erythema and pruritus in a subset of patients and decreased *Staphylococcus aureus* skin colonization.⁴²

Systemic Therapies

The advent of new biologic and oral medications for AD has revolutionized therapy for patients with moderate-to-severe AD.

Patient Selection

Numerous factors should be considered before the initiation of systemic therapy for patients with AD, including disease severity, impact on quality of life, and risks vs benefits (Fig 1). The International Eczema Council published a consensus statement in 2017 with an algorithm for determining when to consider systemic therapy for patients with moderate-to-severe AD, specifically after evaluation for alternative diagnoses, optimization of topical treatments, adequate patient education, and consideration of phototherapy.⁴³ Systemic therapy should be considered for patients with severe or recalcitrant disease, especially if there is a considerable negative impact on quality of life.⁴⁴ With the FDA approval of newer biologics and immunomodulators for the treatment of AD, the threshold for systemic therapy initiation may be lowered. These newer agents have more specific targets for AD that result in more favorable safety profiles and require less monitoring compared with traditional immunosuppressive therapies (Fig 2).

Traditional Immunosuppressive

As older AD therapies are still used in practice, they merit a brief discussion. Systemic agents traditionally used to treat severe or difficult-to-control AD include Cyclosporine, Azathioprine, Methotrexate, and Mycophenolate Mofetil. None of these agents are FDA approved for the treatment of AD, and there is variability of efficacy in AD. In addition, these agents have multiple known adverse effects, require

consistent laboratory monitoring, and have special consideration regarding vaccination.⁴³ Continuous oral steroids are not recommended for routine management of patients with AD, but they may be considered as short-term therapy in patients with severe, refractory disease.⁴³

Biologics

Biologics have changed the landscape of AD treatment by offering increased efficacy, fewer adverse effects, and less frequent dosing compared with other systemic agents. The most widely used and investigated biologic for AD is dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling, key drivers of type 2 inflammation in AD. Dupilumab is the first biologic to receive FDA approval in 2017 for moderate-to-severe AD in adults. In clinical trials investigating dupilumab as monotherapy (SOLO1 and SOLO2), 36% to 38% of treated patients achieved Investigator's Global Assessment (IGA) scores of 0 (clear) or 1 (almost clear) compared with placebo (8%–10%) ($P < .001$).⁴⁵ In 2019, dupilumab was subsequently approved in adolescents based on phase 3 trial results revealing an improvement of Eczema Area and Severity Index (EASI) scores, with more patients having a 75% improvement in EASI score (EASI-75) in the treated group compared with placebo, and higher attainment of IGA of 0 to 1 in the treated group compared with placebo.⁴⁶

In 2020, the age indication was expanded to include children as young as 6 years old, which makes dupilumab the first biologic approved for AD in this patient population. This approval was based on results in the phase 3 trial (LIBERTY AD PEDS; $n = 367$) in children aged 6 to 11 years.⁴⁷ In the study, 75% of the treated group (dupilumab plus TCSs) achieved EASI-75 at 16 weeks compared with 26% to 28% of the placebo group (TCSs alone) ($P < .001$).⁴⁷ Moreover, dupilumab has been studied in younger children; recent results from a phase 2 pivotal trial (LIBERTY AD PRE-SCHOOL) in children aged 6 months to 6 years old with severe, uncontrolled AD revealed that dupilumab met all primary and secondary end points.⁴⁸

To date, dupilumab has had an excellent safety profile, with the most common adverse effects being conjunctivitis and injection site reactions; most cases of conjunctivitis were mild-moderate and resolved during the treatment period.⁴⁹ In addition, tuberculosis testing and laboratory monitoring are not required, making it particularly advantageous for the pediatric population.⁴⁹ Dupilumab is also FDA approved for the treatment of moderate-to-severe asthma in ages 6+ years and chronic rhinosinusitis with nasal polyposis in adults, 2 disorders with overlap with AD.⁵⁰ Indeed, dupilumab has certainly revolutionized AD treatment with its sustained long-term efficacy in patients with moderate-to-severe AD.

Further insights into the immunology of AD have sparked drug development with more than 25 different biologics on the horizon. Tralokinumab, a specific anti-IL-13 agent, received approval in December 2021 for adults, and lebrikizumab (anti-IL-13) and nemolizumab (anti-IL-31) are furthest along in the clinical trials. In 2 long-term phase III monotherapy studies (ECZTRA 1 and ECZTRA 2), subcutaneous tralokinumab 300 mg every other week was deemed superior to placebo at 16 weeks of treatment with 16% (ECZTRA 1) and 22% (ECZTRA 2) of patients achieving IGA 0/1 scores vs 7% and 11% in respective placebo groups.⁵¹ With continued tralokinumab treatment, most responders maintained improvement even at week 52. The drug was well tolerated with adverse effects comparable with that of placebo and with improvements in sleep, pruritus, and quality of life.⁵¹

Another monoclonal antibody targeting IL-13 is lebrikizumab. In a phase IIb trial, 280 patients were randomized to placebo or subcutaneous lebrikizumab at varying doses of 125 mg every 4 weeks, 250 mg every 4 weeks, or 250 mg

every 2 weeks. At week 16, lebrikizumab-treated groups had dose-dependent, improvements in EASI scores and pruritus Numerical Rating Scale (NRS) compared with placebo.⁵² Lebrikizumab phase III trial results revealed good efficacy in unpublished data.

Nemolizumab is an innovative biologic that targets the IL-31 receptor, an important component of the itch response. Results from a phase IIb study reported that nemolizumab had an acceptable safety profile and improved EASI, IGA, and NRS-itch scores, with maximal efficacy observed at 30 mg. The most common adverse events were nasopharyngitis and upper respiratory tract infections.⁵³

Oral JAKs

Until 2022, the only FDA-approved oral medication for AD was oral Prednisone,⁵⁴ which comes with severe safety concerns related to long-term use. The recent FDA approval of the oral JAKi's Upadacitinib (currently approved for ages 12+ years)⁵⁴ and Abrocitinib (currently approved for ages 18+ years)⁵⁴ adds additional, efficacious oral options for patients with moderate-to-severe disease. Baricitinib is an additional forthcoming JAKi which has been found to have good long-term efficacy and is currently used for AD therapy internationally, but it is not yet FDA approved for the treatment of AD.⁵⁵

In the 52-week Measure Up 1 and Measure Up 2 trials of Upadacitinib monotherapy, patients receiving both 15 mg daily and 30 mg daily oral Upadacitinib had improvements in EASI and IGA compared with placebo. There was rapid onset improvement in patient's Worst Pruritus Numeric Rating Scale, with both arms experiencing improvement within 2 weeks of use and itch improvement nearing peak values by 4 weeks of use.⁵⁶ The JADE MONO-1 study evaluated Abrocitinib monotherapy at either 100 mg daily or 200 mg daily dose compared with placebo. This study revealed similar, though less dramatic, results as the Upadacitinib studies, with both doses of Abrocitinib leading to improvements in itch and EASI and IGA scores compared with placebo.⁵⁷

The JADE COMPARE⁵⁸ and Heads Up⁵⁹ studies help assess the efficacy of JAK inhibitors against dupilumab. In the JADE Compare study, patients were randomized to 1 of 2 doses of abrocitinib, dupilumab, or placebo. Abrocitinib was superior to dupilumab in itch response at week 2. However, by 16 weeks, neither dose differed significantly from dupilumab in most other secondary end points.⁵⁸ The Heads Up study revealed the superiority of 30 mg daily Upadacitinib compared with 300 mg dupilumab every other week in both itch scores and severity outcome measures.⁵⁹ Patients receiving Upadacitinib had greater improvement in itch as early as week 1 and experienced both more rapid and greater improvement in EASI scores compared with patients receiving dupilumab.⁵⁹ It should be noted that the FDA approval of Upadacitinib suggests the use of the lower dose of Upadacitinib, 15 mg initially, which was not studied in the Heads Up protocol.

Although the approved oral JAK inhibitors have been found to be efficacious agents with relatively quick onset of improvement, there are concerns as to the safety and labeling of these new medications. Abrocitinib is associated with nausea, acneiform eruptions, and herpes zoster.⁵⁸ Upadacitinib is associated with increased rates of acne, serious infections, eczema herpeticum, herpes zoster, and laboratory-related adverse events, including transaminase elevations, anemia, and neutropenia.⁵⁹

More important is understanding of the black box warning associated with JAKis as a class of medications, both oral and topical. Tofacitinib, a JAKi approved for use in rheumatoid arthritis, has been found in long-term safety studies to be associated with increased risk of blood clots, heart-related events, cancer, and death, including opportunistic infections.⁶⁰ This finding has led to black box labeling of the

class of medications, though to date, many of these same findings have not been found in studies of patients with AD.^{59,60} Further studies are required to evaluate the long-term effects of these drugs in patients with AD; however, physicians should be aware of these labels to select appropriate candidates for therapy and properly counsel patients.

Special Considerations

Multidisciplinary Approach

Improved understanding of disease pathways and development of new therapeutic options has increased the complexity of diagnosis and treatment for many fields, including those who treat atopic disorders. Understanding of the type 2 inflammatory pathway has revealed the interconnectedness of atopic disorders and highlighted a need for coordination of care between specialties that treat atopic conditions. For AD, this could include evaluation by a dermatologist and allergist alongside psychological support, nutritional assessment, and patient education.⁶¹

There are several multidisciplinary centers across the country that have formed to address the need for more comprehensive care for patients with moderate-to-severe AD. In addition to medical evaluation by specialists trained to treat AD, such as dermatologist and allergists, many of the programs include robust education programs. The multidisciplinary program at the National Jewish Health includes demonstration of skin care techniques, classroom teaching, group therapy, and written materials as part of their patient education.⁶¹ Other programs use group education and support sessions at patient-provider clinics.⁶² Several multidisciplinary clinics revealed substantial improvements in standardized AD severity measurements and quality-of-life surveys.⁶² Multidisciplinary approaches to AD are important as we acknowledge the complex nature and multiple factors affecting disease control.

Associated Diagnoses

On the basis of observations of “overlap” disorders with AD and the diverse clinical presentations and phenotypes of AD, a consensus group proposed the term “Atopic Dermatitis Spectrum Disorder” to encompass dermatologic disorders that share AD as a common underlying etiology.⁶³ The following 12 distinct diseases were identified as part of the AD spectrum disorder: prurigo nodularis, chronic hand eczema (excluding contact dermatitis), lichen simplex chronicus, nummular eczema, follicular eczema, lichenoid eczema, dyshidrosis, nipple eczema, asteatotic eczema, gestational eczema, eczema of older adults (excluding mycosis fungoides), and eyelid dermatitis (excluding contact dermatitis). However, this list is not comprehensive. These conditions may overlap in clinical features, epidemiology, histology, comorbidities, treatment responses, or pathophysiology.⁶³

Chronic hand eczema, which can be found with or without concurrent or historic AD,⁶³ is a target for new therapeutics that are under investigation. These include the systemic agent guselkumab (Clinicaltrials.gov identifier NCT03728504) and topicals such as ARQ-252 (Clinicaltrials.gov identifier NCT04378569) and delgocitinib (Clinicaltrials.gov identifiers NCT04872101, NCT04871711).

Conclusion

AD is a common disease, associated with quality of life burdens affecting patients across the age spectrum. Improved understanding of pathophysiological mechanisms, comorbidities, and the development of multiple new topical and systemic therapeutic agents is revolutionizing disease management.

References

- Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338–351.
- Bannister MJ, Freeman S. Adult-onset atopic dermatitis. *Australas J Dermatol*. 2000;41(4):225–228.
- Paternoster L, Savenije OEM, Heron J, Evans DM, Vonk JM, Brunekreef B, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J Allergy Clin Immunol*. 2018;141(3):964–971.
- Kim JP, Chao LX, Simpson EL, Silverberg JL. Persistence of atopic dermatitis (AD): a systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75(4):681–687. e11.
- Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM, et al. American Academy of Dermatology Guidelines: awareness of comorbidities associated with atopic dermatitis in adults. *J Am Acad Dermatol*. 2022;86(6):1335–1336. e18.
- Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. *J Am Acad Dermatol*. 2008;58(1):68–73.
- Silverberg JL, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Ann Allergy Asthma Immunol*. 2018;121(5):604–612. e3.
- Waldman AR, Ahluwalia J, Udkoff J, Borok JF, Eichenfield LF. Atopic dermatitis. *Pediatr Rev*. 2018;39(4):180–193.
- Samady W, Warren C, Kohli S, Jain R, Bilaver L, Mancini AJ, et al. The prevalence of atopic dermatitis in children with food allergy. *Ann Allergy Asthma Immunol*. 2019;122(6):656–657. e1.
- Singh AM, Anvari S, Hauk P, Lio P, Nanda A, Sidbury R, et al. Atopic dermatitis and food allergy: best practices and knowledge gaps—a work group report from the AAAAI allergic skin diseases committee and leadership institute project. *J Allergy Clin Immunol Pract*. 2022;10(3):697–706.
- Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803–813.
- Chang A, Robison R, Cai M, Singh AM. Natural history of food-triggered atopic dermatitis and development of immediate reactions in children. *J Allergy Clin Immunol Pract*. 2016;4(2):229–236. e1.
- Eapen AA, Kloepfer KM, Leickly FE, Slaven JE, Vitalpur G. Oral food challenge failures among foods restricted because of atopic dermatitis. *Ann Allergy Asthma Immunol*. 2019;122(2):193–197.
- Miyaji Y, Yang L, Yamamoto-Hanada K, Narita M, Saito H, Ohya Y. Earlier aggressive treatment to shorten the duration of eczema in infants resulted in fewer food allergies at 2 years of age. *J Allergy Clin Immunol Pract*. 2020;8(5):1721–1724. e6.
- Batchelor JM, Ridd MJ, Clarke T, Ahmed A, Cox M, Crowe S, et al. The Eczema Priority Setting Partnership: a collaboration between patients, carers, clinicians and researchers to identify and prioritize important research questions for the treatment of eczema. *Br J Dermatol*. 2013;168(3):577–582.
- Ronnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;79(3):448–456. e30.
- Silverberg JL, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. adults. *Br J Dermatol*. 2019;181(3):554–565.
- Kern C, Wan J, LeWinn KZ, Ramirez FD, Lee Y, McCulloch CE, et al. Association of atopic dermatitis and mental health outcomes across childhood: a longitudinal cohort study. *JAMA Dermatol*. 2021;157(10):1200–1208.
- Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2013;131(2):428–433.
- Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med*. 2005;159(8):745–750.
- Moore K, David TJ, Murray CS, Child F, Arkwright PD. Effect of childhood eczema and asthma on parental sleep and well-being: a prospective comparative study. *Br J Dermatol*. 2006;154(3):514–518.
- Yang EJ, Beck KM, Sekhon S, Bhutani T, Koo J. The impact of pediatric atopic dermatitis on families: a review. *Pediatr Dermatol*. 2019;36(1):66–71.
- Brunner PM, Suarez-Farinas M, He H, Malik K, Wen H-C, Gonzalez J, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. *Sci Rep*. 2017;7(1):8707.
- Kantor R, Kim A, Thyssen JP, Silverberg JL. Association of atopic dermatitis with smoking: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75(6):1119–1125. e1.
- Silverberg JL, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. *J Allergy Clin Immunol*. 2015;135(3):721–728. e6.
- Zhang A, Silverberg JL. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. *J Am Acad Dermatol*. 2015;72(4):606–616. e4.
- Silverwood RJ, Forbes HJ, Abuabara K, Ascott A, Schmidt M, Schmidt SAJ, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *BMJ*. 2018;361:k1786.
- Ascott A, Mulick A, Yu AM, Prieto-Merino D, Schmidt M, Abuabara K, et al. Atopic eczema and major cardiovascular outcomes: a systematic review and meta-analysis of population-based studies. *J Allergy Clin Immunol*. 2019;143(5):1821–1829.

29. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116–132.
30. van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. *Cochrane Database Syst Rev*. 2017;2(2):CD012119.
31. Chiang C, Eichenfield LF. Quantitative assessment of combination bathing and moisturizing regimens on skin hydration in atopic dermatitis. *Pediatr Dermatol*. 2009;26(3):273–278.
32. Luger T, Paller AS, Irvine AD, Sidbury R, Eichenfield LF, Werfel T, et al. Topical therapy of atopic dermatitis with a focus on pimecrolimus. *J Eur Acad Dermatol Venerol*. 2021;35(7):1505–1518.
33. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol*. 2006;54(1):1–15.
34. Salava A, Perälä M, Pelkonen A, Mäkelä M, Remitz A. Safety of tacrolimus 0.03% and 0.1% ointments in young children with atopic dermatitis: a 36-month follow-up study. *Clin Exp Dermatol*. 2022;47(5):889–902.
35. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. *Nat Rev Drug Discov*. 2022;21(1):21–40.
36. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. 2016;75(3):494–503. e6.
37. Schlessinger J, Shepard JS, Gower R, Su JC, Lynde C, Cha A, et al. Safety, effectiveness, and pharmacokinetics of crisaborole in infants aged 3 to <24 months with mild-to-moderate atopic dermatitis: a phase IV open-label study (CrisADE CARE 1). *Am J Clin Dermatol*. 2020;21(2):275–284.
38. Gong X, Chen X, Kuligowski ME, Liu X, Liu X, Cimino E, et al. Pharmacokinetics of Ruxolitinib in patients with atopic dermatitis treated with Ruxolitinib cream: data from phase II and III studies. *Am J Clin Dermatol*. 2021;22(4):555–566.
39. Furue M. Regulation of filaggrin, loricrin, and involucrin by IL-4, IL-13, IL-17A, IL-22, AHR, and NRF2: pathogenic implications in atopic dermatitis. *Int J Mol Sci*. 2020;21(15):5382.
40. Furue M, Hashimoto-Hachiya A, Tsuji G. Aryl hydrocarbon receptor in atopic dermatitis and psoriasis. *Int J Mol Sci*. 2019;20(21):5424.
41. Forte Bioscience. Clinical trial of FB-401 for the treatment of atopic dermatitis fails to meet statistical significance. Available at: <https://www.fortebiorx.com/investor-relations/news/news-details/2021/Clinical-Trial-of-FB-401-For-the-Treatment-of-Atopic-Dermatitis-Fails-to-Meet-Statistical-Significance/default.aspx>. Accessed May 2, 2022.
42. Nakatsuji T, Hata TR, Tong Y, Cheng JY, Shafiq F, Butcher AM, et al. Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial. *Nat Med*. 2021;27(4):700–709.
43. Simpson EL, Bruin-Weller M, Flohr C, Arden-Jones MR, Barbarot S, Deleuran M, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol*. 2017;77(4):623–633.
44. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71(2):327–349.
45. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335–2348.
46. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156(1):44–56.
47. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *J Am Acad Dermatol*. 2020;83(5):1282–1293.
48. Paller AS, Siegfried EC, Simpson EL, Cork MJ, Lockshin B, Kosloski MP, et al. A phase 2, open-label study of single-dose dupilumab in children aged 6 months to <6 years with severe uncontrolled atopic dermatitis: pharmacokinetics, safety and efficacy. *J Eur Acad Dermatol Venerol*. 2021;35(2):464–475.
49. Wollenberg A, Beck LA, Blauvelt A, Simpson EL, Chen Z, Chen Q, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). *Br J Dermatol*. 2020;182(5):1120–1135.
50. US Food and Drug Administration. DUPIXENT® (dupilumab). Highlights of prescribing information. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014bl.pdf. Accessed May 2, 2022.
51. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour J-P, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol*. 2021;184(3):437–449.
52. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. *JAMA Dermatol*. 2020;156(4):411–420.
53. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz J-D, Wollenberg A, et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol*. 2020;145(1):173–182.
54. Brunk DFDA. Approves two oral JAK inhibitors for atopic dermatitis. Medscape medical news. 2022. Available at: <https://www.medscape.com/viewarticle/966698>. Accessed March 31, 2022.
55. Silverberg JI, Simpson EL, Wollenberg A, Bissonnette R, Kabashima K, DeLozier AM, et al. Long-term efficacy of baricitinib in adults with moderate to severe atopic dermatitis who were treatment responders or partial responders: an extension study of 2 randomized clinical trials. *JAMA Dermatol*. 2021;157(6):691–699.
56. Simpson EL, Papp KA, Blauvelt A, Chu C-Y, Hong HC-H, Katoh N, et al. Efficacy and safety of Upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the Measure Up 1 and Measure Up 2 randomized clinical trials. *JAMA Dermatol*. 2022;158(4):404–413.
57. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10246):255–266.
58. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384(12):1101–1112.
59. Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2021;157(9):1047–1055.
60. US Food and Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death>. Accessed March 31, 2022.
61. Senna G, Micheletto C, Piacentini G, Schiappoli M, Girolomoni G, Sala G, et al. Multidisciplinary management of type 2 inflammatory diseases. *Multidiscip Respir Med*. 2022;17(1):813.
62. LeBovidge JS, Elverson W, Timmons KG, Hawryluk EB, Rea C, Lee M, et al. Multidisciplinary interventions in the management of atopic dermatitis. *J Allergy Clin Immunol*. 2016;138(2):325–334.
63. Butler DC, Simpson E, Guttman-Yassky E, Eichenfield LF, Golant AK, Koo JYM, et al. The atopic dermatitis spectrum disorder. Recognizing the clinical heterogeneity in patients with atopic related skin conditions in order to improve therapeutic decision-making and outcomes: an expert panel consensus statement. *J Dermatol Treat*. 2021;1–3.