New Horizons in the Treatment and Management of Atopic Dermatitis (AD)

How Novel Therapies are Changing the Treatment Paradigm

A CME CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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New Horizons in the Treatment and Management of Atopic Dermatitis (AD): How Novel Therapies are Changing the Treatment Paradigm

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Dr. Owens is President, Gary Owens Associates.

Learning Objectives:
1. Explore the mechanism of action in novel therapies in the management of atopic dermatitis.
2. Define the research underlying the most current understanding of the pathophysiologic mechanisms of atopic dermatitis.
3. Discuss the role of new therapies that block the IL-4/IL-13 signaling pathway, and how they might be integrated into the evolving treatment paradigm.
4. Compare and contrast the safety and efficacy of new therapies in the management of moderate-to-severe AD.
5. Identify the latest research regarding the development of therapeutic agents that address the pathophysiologic mechanisms of atopic dermatitis.
6. Discuss methods to enable optimal cost management of emerging therapies to be realized by multiple AD stakeholders including managed care organizations.

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Post-Test Questions

1. Which of the following is an accurate statement about atopic dermatitis in the U.S.?
   a. About 7 million in the U.S. are affected by AD.
   b. Mild disease is most common in children.
   c. Approximately one of three children with AD has moderate-to-severe disease.
   d. About ten percent of U.S. adults with AD require systemic therapy.
2. Which of the following is a major factor in maintaining an intact skin barrier.
   a. Filaggrin b. Collagen c. Elastin d. Ceramides
3. In Atopic Dermatitis pathogenesis, which of the following is NOT a T helper cell two (Th2) derived cytokine?
   a. Interleukin four (IL-4) b. IL-13 c. IL-31 d. IL-22
4. In patients with AD, even unaffected skin is not normal.
   a. True b. False
5. Which of the following NOT a consequence of atopic dermatitis in children?
   a. Impaired sleep.
   b. Long-term impaired learning ability.
   c. Attention deficit hyperactivity disorder.
   d. Impaired health related quality of life.
6. Which of the following should be included in the therapeutic regimen for all levels of atopic dermatitis (mild to severe)?
   a. Topical antihistamines
   b. Systemic immune suppression
   c. Good skin care and moisturization.
   d. Topical antibiotics and antimicrobial skin washes..
7. Which of the following is the most common barrier to use of topical corticosteroids in managing atopic dermatitis in children?
   a. Pain on application b. Cost
   c. Lack of efficacy d. Fear of adverse effects
8. Which of the following is an ACCURATE statement about crisaborole in the management of atopic dermatitis?
   a. It is indicated to treat moderate-to-severe AD in adults and children two years of age and older.
   b. It is a systemic phosphodiesterase type 4 (PDE4) inhibitor.
   c. The most common adverse effects are disease flares, application site pain and infections.
   d. Steroid like adverse reactions, such as application site atrophy and telangiectasia, have occurred.
9. Which of the following is an INCORRECT statement about dupilumab in the management of atopic dermatitis?
   a. It is an IL-4 α receptor antagonist which inhibits signaling of IL-4 and IL-13.
   b. It is indicated for adult and adolescent patients with moderate-to-severe AD.
   c. Dupilumab treatment groups results in an average 35 percent more patients achieving EASI-75 compared with placebo.
   d. It is the first therapy in AD that demonstrates both clinical and molecular disease suppression.
10. Which of the following will likely be instituted by managed care payers to manage utilization of dupilumab and subsequent biologics?
    a. Stepped care b. Prior authorization.
    c. Tiered co-pays d. All of the above

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)

1. Based on the content presented I am better able to:

   Explore the mechanism of action in novel therapies in the management of atopic dermatitis.

   4 3 2 1

   Define the research underlying the most current understanding of the pathophysiologic mechanisms of atopic dermatitis.

   4 3 2 1

   Discuss the role of new therapies that block the IL-4/IL-13 signaling pathway, and how they might be integrated into the evolving treatment paradigm.

   4 3 2 1

   Compare and contrast the safety and efficacy of new therapies in the management of moderate-to-severe AD.

   4 3 2 1

   Identify the latest research regarding the development of therapeutic agents that address the pathophysiologic mechanisms of atopic dermatitis.

   4 3 2 1

   Discuss methods to enable optimal cost management of emerging therapies to be realized by multiple AD stakeholders including managed care organizations.

   4 3 2 1

2. The activity met my expectations. 4 3 2 1
3. The activity and presenters were free of bias. 4 3 2 1
4. The activity was applicable to my position. 4 3 2 1
5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)

   4 3 2 1

6. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

7. What other topics interest you? _____
8. My goal of participating in this activity was: _____

   _____

9. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

10. Due to the content of this activity, I will change my practice patterns by:

    ☐ Identifying opportunities to improve treatment options for patients.
    ☐ Providing guidelines and resources on new therapies to providers.
    ☐ My practice patterns will not change.
    ☐ Other (specify): _____

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.

    ☐ Management and leadership skills
    ☐ Business and/or financial expertise to manage the medical loss ratio.
    ☐ Exchange ideas and network with colleagues to improve patient outcomes.
    ☐ Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
    ☐ Clear knowledge of practice of medicine, especially common disease.
    ☐ Stay updated on clinical conditions.

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Lawrence F. Eichenfield, MD; Emma Guttman-Yassky, MD, PhD, FAAD; Adelaide A. Hebert, MD; Gary M. Owens, MD

Introduction

ATOPIC DERMATITIS (AD) IS THE MOST common chronic inflammatory skin disease, often starting in childhood. It is the most common type of eczema and manifests as eczematous rashes, itch, bacterial colonization and secondary infections. It can have an intermittent or persistent course.[1] Other types of eczema include contact dermatitis, dyshidrotic eczema, neurodermatitis, nummular eczema, and stasis dermatitis.[2]

Depending on the country, AD occurs in 15 to 30 percent of children and 3 to 10 percent of adults.[3-5] In children, 45 percent of cases begin within the first six months of life, 60 percent begin during the first year, and 85 percent before five years of age. Up to 70 percent of children have spontaneous remission of AD before adolescence, but the rest will have continued AD into adulthood. Adult onset AD can also occur.

It is estimated that 31.6 million people in the United States (U.S.) are affected by AD, with 17.8 million having moderate-to-severe AD.[6] AD is much more common than psoriasis, which only affects 7.4 million U.S. adults.[7] Approximately one out of every three children with AD has moderate-to-severe disease.[6] About 3 percent of U.S. adults have moderate-to-severe AD requiring systemic therapy.[6]

The rates of AD vary by country and within individual countries. Rates are much higher in children in industrialized countries and in those living in urban areas compared with rural, nonindustrialized regions. Rates increase with "westernization" or emigration to industrialized areas.[8] Thus, environmental triggers may play a role in development of AD.

Clinical Presentation/Diagnosis

The disease is characterized by the presence of dry and scaly patches on the skin of the scalp, forehead, and face, particularly the cheeks, flexor surfaces of arms, feet, and legs. (Exhibit 1). AD lesions are characterized by intensely pruritic, erythematous papules associated with excoriation and serous exudation.

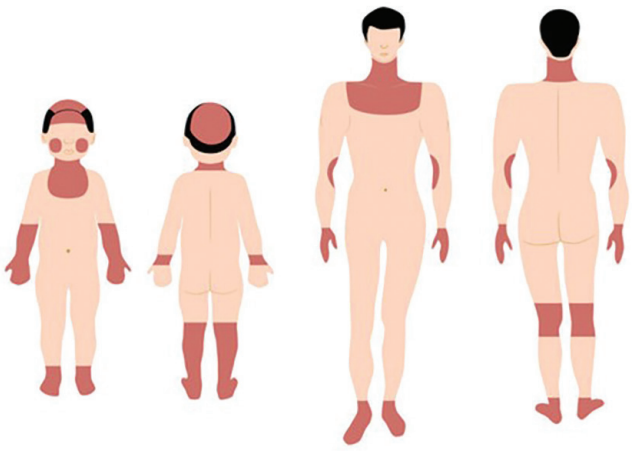
Generally, the diagnosis of AD is made by clinical assessment, but it is often indistinguishable from other causes of dermatitis. In infancy, the most common difficulty is distinguishing it from seborrheic dermatitis (SD). Both SD and AD are associated with cradle cap. Other areas of involvement in SD are the intertriginous areas and diaper area. Erythema and a greasy scale can be seen over the eyebrows and the sides of the nose. In AD, xerosis of the skin and pruritus occur, which are not usually features of SD. Both conditions have to be distinguished from psoriasis.

Pathogenesis

An intact, healthy skin barrier is a critical first line of defense against various microbes, irritants, and allergens. A major factor in maintaining an intact skin barrier is filaggrin.[9] Filaggrin is derived from a protein precursor known as profilaggrin which undergoes proteolytic processing to yield individual filaggrin monomers at the transition between the stratum granulosum and the stratum corneum in the skin. Filaggrin monomers are incorporated into the lipid envelope, which is responsible for the skin barrier function. Filaggrin undergoes further processing in the upper stratum corneum to release free amino acids that assist in water retention.

Atopic dermatitis is thought to be the result of immune dysregulation. In AD, the local expression of cytokines and chemokines orchestrates the progression of skin lesions. Immunologic "priming" of

Exhibit 1: Common Sites of Atopic Dermatitis in Children and Adults



naïve T helper cells is part of the early pathogenesis. With dysregulation of T helper cell 1 and 2 (Th1, Th2) mediated cytokines occurs. T helper cell two (Th2) factors that play a role in AD include interleukin four (IL-4), IL-13, and IL-31. IL-4 and IL-13 are elevated in acute and chronic skin lesions of AD. Patients with AD have increased numbers of CD4- and CD8+ cells that release these two cytokines which have a common receptor, IL-4Rα. High levels of IL-4 and IL-13 act as inhibitors of filaggrin gene expression and antimicrobial peptides in the skin.

In AD, there is decreased filaggrin due to genetic mutations and Th2 mediated down regulation which results in increased epidermal hyperplasia and decreased lipid barrier in the skin. The most immediate result of filaggrin deficiency in AD is decreased stratum corneum hydration. In addition, filaggrin breakdown products play an important role in acidifying the stratum corneum. An increase in the pH of the stratum corneum activates a number of serine proteases. A pH-induced increase in serine protease activity leads to both barrier breakdown and precipitates additional Th2 inflammation.[10]

Mutations in the filaggrin gene (FLG) have been identified.[11] Null mutations in the FLG are a predisposing factor for early-onset AD which persists into adulthood. Loss-of-function genetic variants of FLG (R510X and 2282del4) are also strong predisposing factors for AD.[12] These variants also show a significant association with asthma occurring in context of AD

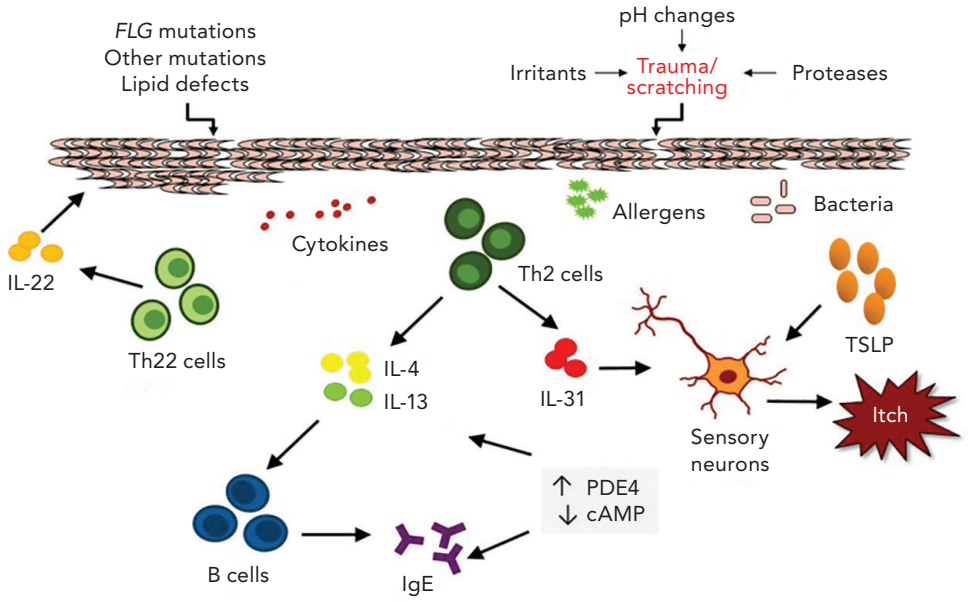
The epidermis of AD patients is characterized by significant barrier disruption. As shown in Exhibit 2, pH changes in the skin, alterations in proteases, and irritants lead to scratching and skin trauma. This skin trauma can allow allergens and bacteria to cross the skin barrier. Without adequate moisture, the skin is dry, red, and readily irritated. It is helpful to think of the barrier defects in AD as resembling a whiffle ball covered with holes that let the water in the skin "out" and the trigger factors "in." The skin barrier abnormality in AD is not just an epiphenomenon (a secondary or additional symptom or complication arising during the course of a malady), it is the initiator of the pathogenesis of the disease state.

In patients with AD, even unaffected skin is not normal. It commonly displays increased dryness and a greater irritant response than the skin of healthy controls. In addition, the unaffected skin of patients with AD—but not skin from healthy controls—displays a sparse perivascular T-cell infiltrate and an increase in the number of Th2 cells.

In chronic lichenified skin lesions of AD—characterized by thick, leathery skin—the tissue has actually undergone remodeling triggered by chronic inflammation. These altered epidermal cells contain increased levels of immunoglobulin E (IgE) bearing Langerhans cells and inflammatory dendritic epidermal cells.[13] Macrophages dominate the dermal infiltrate. Eosinophils contribute to the inflammatory response and T cells remain active.

Overall, two major biologic pathways contribute to the pathophysiology of AD - skin epithelial barrier function and innate/adaptive immune responses.[14] The dysfunctional epidermal barrier and immune

Exhibit 2: Immune Dysregulation in Atopic Dermatitis



cAMP = cyclic adenosine monophosphate
FLG = filaggrin gene
IgE = immunoglobulin E
IL = interleukin
PDE4 = phosphodiesterase four
Th2 = T helper cell two
TSLP = thymic stromal lymphopoietin

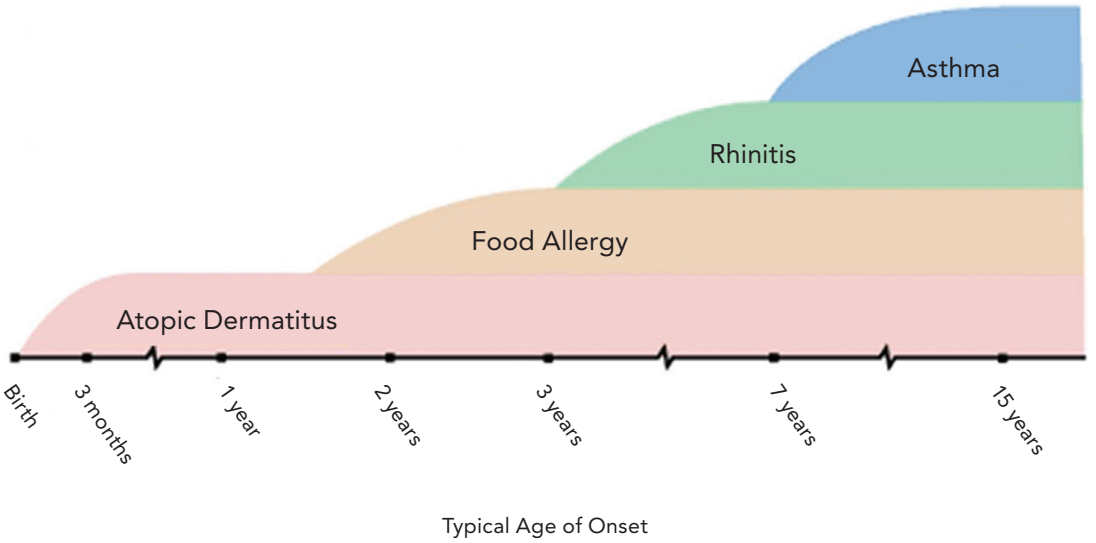
responses reciprocally affect each other, and thereby drive development of AD. Filaggrin plays an essential role in maintaining skin moisture and pH. Filaggrin production is down-regulated by inflammatory mediators such as IL-4 and IL-13. These pathways are potential new targets for AD treatment.

Atopic March

AD is associated with other atopic or allergic diseases. The cutaneous manifestations of atopy in AD often represent the beginning of the atopic march – which is the progression from AD to food allergies, allergic rhinitis, and asthma (Exhibit 3).[15,16] On the basis of several longitudinal studies, approximately half of AD patients will develop asthma, particularly with severe AD, two-thirds will develop allergic rhinitis, and some will have both.[16] In a cross-sectional study of 2,270 children with AD, nearly 80 percent reported another form of allergy (asthma, allergic rhinitis, animal allergies, food allergies, or medication allergies).[17] Epicutaneous sensitization of T cells has been thought to be responsible, with subsequent migration of sensitized T cells into the nose and airways, causing upper and lower airway disease.

Research groups are attempting to determine the early onset AD phenotype in children as compared to adults with similar disease severity. There is early and potent Th2 activation in the blood and skin of children with AD, establishing the systemic nature of new onset AD. In one study, blood and skin samples from 20 children less than five years old, and within six months of disease onset, were compared with samples from 14 age-matched controls.[18] Th2 cytokines were greatly increased in children with AD. Adults with AD maintain an excess Th2 population. In pediatric AD, the Th2 imbalance was confined to skin homing cells and did not extend to CD8 positive populations. Adults extend the Th2 imbalance into systemic T cells as well as CD8 positive T cells.[18] No Th1, Th22, Th17 or Th9 subset expansion was seen in blood of AD children. The selective activation of Th2 in blood may direct B cells toward IgE class switching. This may be another explanation for the atopic march that follows the development of AD. Researchers are questioning if the atopic march can be prevented by appropriate immune manipulations (using broad or specific T-cell targeting) once AD has developed. Unlike psoriasis, an abnormal cytokine profile already exists in non-lesional AD skin.[19] The emerging understanding of the systemic immune dysfunction in AD emphasizes the need

Exhibit 3: TheAtopic March[15,16]



for systemic treatment approaches for severely affected patients.

Consequences of AD

A major symptom of AD is intense pruritus, which is one of the most challenging aspects of disease management. It is the one aspect of AD that most bothers parents of children with AD. Impaired skin barrier facilitates the entry of irritants and itch causing agents. A reduction in skin hydration by 10 percent is crucial for the induction of itch.[20]

Nighttime loss of sleep due to itching and scratching is an issue for both children and their parents. Children may wake up an average of 36 times nightly. Parents of children with AD lose one to one and a half hours of sleep every night. Loss of deep sleep means less growth hormone is secreted with potential for impairment of linear growth. Lack of sleep also means poor coping strategies the next day, impaired school performance, and behavioral issues. Adults with AD with impaired sleep are compromised in their ability to perform certain activities of daily living.

Importantly, AD, like other systemic inflammatory diseases, has impact on mortality.[21,22] In adults, 10-year mortality is increased post hospitalization for AD compared to the general population, but reduced compared to psoriasis.[23] There is also an increased risk of coronary artery disease and myocardial infarction with moderate-to-severe AD.[24,25]

Results from multiple studies demonstrate that AD has an impact on health-related quality of life (HRQoL), particularly on social functioning and psychological well-being.[26] There is a greater HRQoL impact with greater disease severity. AD has as large an impact on HRQoL as several chronic conditions and other dermatologic conditions.

Mental health issues related to AD include depression, anxiety, and attention deficit hyperactivity disorder (ADHD) in younger children. Approximately one in five adults with AD meet the diagnostic criteria for major depression.[27] There is a relationship between severity of AD and the prevalence of ADHD.[28] Other issues that can occur with severe AD include abscesses, cellulitis, sepsis, osteomyelitis, and bacterial colonization. Fortunately, these issues are rare.

Costs of AD Treatment

Overall, health-related costs of AD were estimated at 5.2 billion U.S. dollars in 2015; this was an increase from 3.8 billion in 2002.[29,30] The per patient monthly cost was $349 in 2015 and is increasing with newly available medications. Total hospitalization costs of AD in the U.S. have been reported to be $8.2 million per-year for adults and $3.3 million for children.[31] Eighty-six percent of pediatric dermatology admissions to the hospital are for AD. Thus, in addition to symptom burden and impact on mortality, AD is a costly disease to manage.

Interventions/Treatments

The most effective therapy of AD includes short-term treatment of disease flares and a long-term maintenance approach to skin care designed to prevent or minimize flares. The American Academy of Dermatology publishes clinical care guidelines for AD which address use of nonpharmacologic, topical, and systemic therapies.[32,33] It is important to note that the majority of studies with AD treatments are in adults. A few agents have some pediatric data. There is a large unmet need for safe and effective therapeutics in both adults and children.

Skin Care

Good skin care is the first-line intervention for AD. Bathing is suggested for patients with AD as part of treatment and maintenance; however, there is no standard for the frequency or duration of bathing appropriate for those with AD.[32] The addition of oils, emollients, and most other additives to bath water are not recommended. Limited use of non-soap cleansers (neutral to low pH, hypoallergenic, and fragrance free) is recommended.

An integral part of good skin care is the application of moisturizers/emollients. There is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.[32] Moisturizers are part of maintenance care for all levels of AD, and the primary intervention for mild AD in infants. Moisturizers are applied soon after bathing to improve skin hydration in patients with AD. Use of wet-wrap therapy with or without a topical corticosteroid can be recommended for patients with moderate-to-severe AD to decrease disease severity and water loss during flares.

Itching

Good skin moisturization helps reduce itching. Chilled Noxzema™ is one over-the- counter product which can be used to control itching. As a counterirritant, it replaces the sensation of itching with a cooling, tingling sensation and can be applied as often as needed, does not need to be washed off, and is cost effective for managing itching.

Antihistamines do not adequately control the itching associated with AD and are not recommended for routine use in managing AD.[33] Sedative effects of antihistamines are beneficial for helping children sleep and allowing the family get the rest they need, but short-term, intermittent use of sedating antihistamines for sleep should not be substituted for AD management with appropriate therapies.[33] Topical antihistamines are not recommended because of the risk of absorption and contact dermatitis.[32]

Topical Corticosteroids

Topical corticosteroids have been the mainstay of therapy for AD. Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. As an anti-inflammatory, they are used for acute flare management and intermittently for maintenance therapy. There are seven classes from mild to super-potent and, in general, the order of potency is, hydrocortisone > desonide > mometasone > triamcinolone > fluocinonide > betamethasone > clobetasol.

A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of AD including patient age, affected areas of the body, degree of xerosis, patient preference, and cost of medication. Mid-potency agents are the workhorses of management. Low-potency agents should be used on delicate skin areas including the face and genitals. Low-potency topical corticosteroids generally are safe for short-term use. There are concerns about using the more potent agents and/or long-term use of any agents. Refractory lesions and tough-to-treat areas (hands and feet) may require super-potency agents.

There are many methods of use from which to choose, starting with low potency and working upward, to starting with high potency and decreasing potency once controlled. Twice-daily application of corticosteroids is generally recommended for the treatment of acute AD flares. Proactive, intermittent use of topical corticosteroids as maintenance therapy (1-2 times/week) on areas that commonly flare is recommended. The cost of generic topical corticosteroids has skyrocketed in the past decade. Patients often have high co-pays and may not be able to get the preferred topical steroid.

The potential for both skin and systemic side effects, including possible hypothalamic-pituitary-adrenal (HPA) axis suppression, should be considered. HPA axis suppression following systemic absorption of topically applied corticosteroids is a serious systemic complication, but fortunately it is rare. However, use of high-potency steroids carries a great risk for suppression. Monitoring for cutaneous side effects during long-term, potent steroid use is recommended. Cutaneous adverse effects include skin atrophy, telangiectasia, steroid-induced acne/perioral dermatitis, and striae (stretch marks), which are an irreversible complication.

Although rare overall, complications from corticosteroid use can occur at any age. Due to their increased surface area to body weight ratio, children have a higher probability of absorbing corticosteroids, resulting in high blood concentrations

and systemic side effects. In addition, AD often affects the face in infants and small children, a site most subject to local atrophy from topical steroids. Complications of corticosteroid use in children are almost always related to an inappropriate class of steroid for the patient, inappropriate duration of therapy, inappropriate anatomical sites, and the use of occlusive techniques.

A major barrier to adequate treatment of AD with topical corticosteroids is patient or parent fear. Patient fears of side effects associated with the use of topical corticosteroids should be recognized and addressed. In one survey, 72.5 percent of parents worried about putting steroids on their child's skin.[34] Twenty-four percent admitted to not using medicines because of the worries.[34]

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors [tacrolimus (Protopic®) and pimecrolimus (Elidel®)] are also effective in AD. These anti-inflammatory agents were considered breakthrough products when initially introduced. They inhibit calcineurin dependent T-cell activation, blocking the production of pro-inflammatory cytokines in AD. They have also been demonstrated to affect mast cell activation, and tacrolimus decreases both the number and costimulatory ability of epidermal dendritic cells. Extensive clinical trials have shown fair to good efficacy for mild, moderate, and severe AD.

Pimecrolimus cream is indicated as a second-line treatment for the short-term and non-continuous chronic treatment of mild to moderate AD.[35] Tacrolimus ointment, both 0.03 percent and 0.1 percent for adults, and only 0.03 percent for children aged 2 to 15 years, is indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate-to-severe AD in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable.[36]

Pimecrolimus and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Pre-treatment of patients with topical corticosteroids to reduce inflammation should be considered before starting these agents to minimize application site reactions. Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with AD who are applying these agents is not recommended.[32]

Calcineurin inhibitors are potent immunosuppressives when used orally. Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors. Thus, continuous long-term use of topical calcineurin inhibitors, in any age group, should be avoided, and application limited to areas of involvement with AD.[32] When a black box warning about the unknown long- term malignancy risk was added to the product labeling for this class, there was a 70 percent reduction in the use of these agents.

Overall, topical calcineurin inhibitors are recommended and effective for acute and chronic AD treatment.[32] They have the benefit of not causing cutaneous atrophy, with little negative effect on collagen synthesis and skin thickness. The American Academy of Dermatology (AAD) guidelines recommended them for use on actively affected areas as a steroid-sparing agent for the treatment of AD.[32] Proactive, intermittent use of topical calcineurin inhibitors as maintenance therapy (2-3 times per week) on areas that commonly flare is an effective option.[32] Clinical situations in which topical calcineurin inhibitors may be preferable to topical steroids include recalcitrance to steroids, affected sensitive skin areas, steroid-induced atrophy, and long-term uninterrupted topical steroid use.[32]

Crisaborole

Crisaborole (Eucrisa®), a topical benzoxaborole phosphodiesterase type 4 (PDE4) inhibitor, was recently FDA approved for AD. It is indicated to treat mild to moderate AD in adults and children 2 years of age and older. Crisaborole blocks cytokine synthesis by increasing cyclic adenosine monophosphate (cAMP) levels and subsequently protein kinase A levels which negatively modulate signaling pathways that lead to cytokine production.

Crisaborole has a boron ring integrated in its cyclic structure which provides stability and effective target-binding capacity and selectivity. This agent's low molecular weight facilitates penetration through human skin and access to target cells.

Crisaborole is applied to the skin twice a day. Studies have shown that crisaborole reduces inflammation and itching and repairs the skin barrier.[37] This agent results in a 7.4 to 13.4 percent improvement in Investigator Static Global Assessment of clear or almost clear (≥ 2 grade improvement) over placebo at 29 days of treatment.[37]

The most common adverse effects with crisaborole are AD flares and application site pain and infections. These occur is less than 5 percent of patients. The rates of topical adverse effects remained very low over two years of treatment.[37] Steroid-like adverse reactions, such as application site atrophy and telangiectasia, did not occur during the crisaborole studies.

Exhibit 4: Current Treatment Approaches[32,33]

Topical Therapies	Systemic Agents	Biologics	Light Therapies
Emollients	Corticosteroids	Dupilumab*	Narrow band UVB (NBUVB)
Corticosteroids	Antimetabolites • Methotrexate (MTX)		UVA/PUVA
Calcineurin inhibitors* • Tacrolimus • Pimecrolimus	Calcineurin inhibitors • Cyclosporine • Tacrolimis		
Antimicrobials and antiseptics	Inosine monophosphate dehydrogenase inhibitor • Mycophenolate mofetil		
Antihistamines	Purine analog • Azathioprine		
Crisaborole*	Interferon gamma		
	Antibiotics		

* FDA indication for Atopic Dermatitus

There are no comparative efficacy studies with topical corticosteroids or calcineurin inhibitors. The retail price of crisaborole is approximately $710 per 60 gram tube. The cost-effectiveness, effect on sensitive skin regions, efficacy and adverse effects in those under age 2, nor long-term safety with this agent are known. Oral PDE4 inhibitors have been used long term without major adverse effects. These include apremilast (Otezla®) for psoriasis and roflumilast (Daliresp®) for chronic obstructive pulmonary disease.

Topical Treatment Summary

Overall, moisturization and maintenance of an intact skin barrier are essential to managing AD. Topical corticosteroids are generally first line. Topical calcineurin inhibitors may be used with or without topical corticosteroids. Crisaborole is a new topical option for mild to moderate AD. Despite these therapeutic options, treatment of AD often remains suboptimal and patients have to move to systemic therapy.

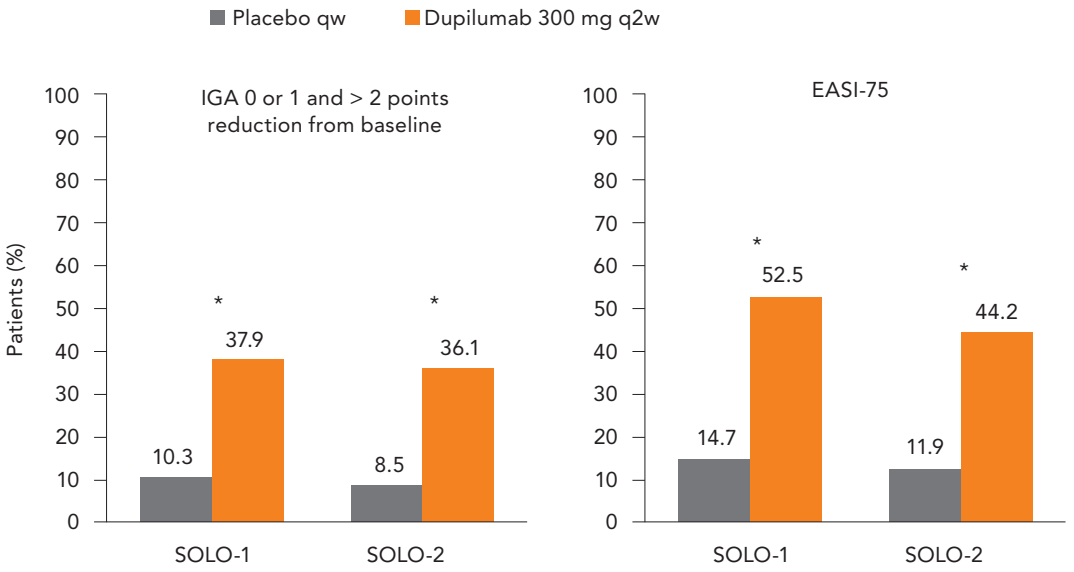
Systemic Agents

Although there are numerous systemic agents which have been used to manage AD that has failed topical therapy and good skin care, not all are FDA approved for such use. Exhibit 4 lists systemic, topical, and phototherapy treatment options and notes which are FDA approved.[32,33] Cyclosporine and oral tacrolimus are the fastest and most powerful when used at appropriate doses, but efficacy can wane over time. Because of long-term immunosuppressive effects, these are not a great option beyond six to 12 months of use. Prednisone is fast and effective but a poor long-term option due to safety. Also, it is possible that prednisone destabilizes the disease after discontinuation. Mycophenolate mofetil has a slow onset and unpredictable response, but is relatively well tolerated for long-term use. Azathioprine and methotrexate have a slow onset of efficacy, but produce robust responses when dosed appropriately. These two agents are good long-term options. Phototherapy, typically narrow band ultraviolet B (NBUVB), has a slower onset, but produces robust responses when dosed appropriately. Phototherapy is likely the safest long-term option, but is inconvenient and costly for patients. A survey of systemic agent use in severe pediatric AD found that cyclosporine and methotrexate were the first- and second-line agents used.[38] In adults, methotrexate is the most commonly used agent.[39]

Issues with Systemic Therapy

The systemic therapies have many more significant adverse effects than the topical therapies for AD. In a study of real-world utilization patterns of systemic immunosuppressants among U.S. adult patients with AD, a great deal of toxicity was documented,

Exhibit 5: Efficacy of Dupilumab in Moderate-to-Severe AD at Week 16 Compared with Placebo[44]



*P < 0.0001 vs Placebo

Only data from 300 mg every 2 weeks shown. Study also included 300 mg every week.

IGA 0 or 1= Investigator Global Assessment clear or almost clear
EASI-75 = Eczema Area and Severity Index 75 percent improvement

especially in a database study that typically poorly captures adverse effects.[39] Documented issues included acute renal toxicity, hepatotoxicity, and bone marrow suppression.

Two main barriers to use of systemic agents are adverse effects and suspected risks for long-term toxicity. Doctors fear prescribing systemic therapy and patients are reluctant to take these agents. Unfortunately, even with systemic therapy, 68 percent of patients still have uncontrolled AD and will discontinue therapy within one year.[38] Among adult AD patients treated with systemic immunosuppressants in the real-world study, use of systemic steroids as rescue therapy was common (72% of cases). For those who used systemic steroids, multiple courses were usually needed. Overall, the traditional systemic therapies do not appear to be especially effective and have significant toxicity.

Targeted Biologic Agents

The revolution in AD treatment has begun with the FDA approval of the first targeted biologic agent for this disease. Dupilumab, a fully human monoclonal antibody targeted therapy, was FDA approved March 28, 2017 with an indication for adult patients with moderate-to-severe AD whose disease is not well controlled with topical prescription therapies or who cannot use topical therapies. It is an IL-4 α receptor antagonist which inhibits signaling of IL-4 and IL-13, the Th2 derived cytokines that are important drivers of AD.

Dupilumab has been studied in the treatment of adults with moderate-to-severe AD as monotherapy and in combination with topical corticosteroids.[40-44] In addition, dupilumab has also shown efficacy in uncontrolled persistent asthma and for chronic sinusitis with nasal polyposis.[45-47]

The FDA approval of dupilumab for AD was based on the results of three randomized Phase III pivotal trials of 2,119 adult patients with inadequately controlled AD.[40,44] In all trials, this agent significantly improved measures of skin clearing (Eczema Area and Severity Index [EASI] and Investigator Global Assessment [IGA]) and severity of disease at 16 weeks compared to placebo. As shown in Exhibit 5, in the two placebo controlled trials, there was a clearing or near clearing of skin lesions among 37.9 percent and 36.1 percent who received injections every two weeks compared with 8.5 and 10.3 percent in the placebo groups.[44] The dupilumab treatment groups had an average 35 percent more patients achieve EASI-75 (75% improvement in rash area and eczema severity) compared with placebo.[44] In AD poorly controlled with topicals, dupilumab reduced peak itch at 16 weeks relative to placebo, improved sleep and HRQoL, and reduced anxiety

Exhibit 6: Selected Investigational Therapies for Atopic Dermatitis

Compound	Target	Route
Q301	CRTH2	Topical
Fevipirant	CRTH2	Oral
Ustekinumab (Stelara®)*	IL-12/IL-23	Subcutaneous injection
Lebrikizumab	IL-13	Subcutaneous injection
Tralokinumab	IL-13	Subcutaneous injection
Secukinumab (Cosentyx®)*	IL-17	Subcutaneous injection
ILV-094	IL-22	Intravenous
Nemolizumab	IL-31	Subcutaneous injection
Pitrakinra	IL-4	Subcutaneous injection
Tofacitinib**	JAK	Topical
Apremilast (Otezla®)*	PDE4	Oral
Roflumilast	PDE4	Topical
OPA-15406	PDE4	Topical

* FDA approved for psoriasis
**Oral approved for rheumatoid arthritis (Xeljanz®)
CRTH2 = prostaglandin D2 receptor
IL = interleukin
JAK = Janus kinase
PDE4 = phosphodiesterase

and depression symptoms.[43,44] All trials showed a favorable safety profile.

In one study, where some patients underwent a skin biopsy, dupilumab treatment resulted in changes in the AD molecular disease profile.[42] It improved the AD signature in a dose-dependent manner, the expression of genes upregulated in AD lesions was decreased in treated patients, and the molecular changes paralleled improvements in clinical scores. Thus, dupilumab is the first therapy in AD that demonstrates clinical and molecular disease suppression.

As a monoclonal antibody, it is given subcutaneously every other week after an initial loading dose. The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week. This agent is available as a 300 mg single-dose prefilled syringe. Common adverse effects in the trials included injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

Studies of dupilumab in pediatric populations with AD are ongoing. Preliminary pharmacokinetic and efficacy data were presented at the AAD meeting earlier this year. Dupilumab appears to have similar efficacy in the 12 to 17 year old population to the adult data.[48] Efficacy data on the younger population (6-11) has not been presented or published.

The list price of dupilumab is $37,000 per year, which is substantially greater than any of the other AD treatments.[49] In a draft evaluation, the Institute for Clinical and Economic Review (ICER) found that compared to usual care, the cost per additional quality of life year (QALY) for dupilumab was estimated to be $97,600, below the commonly-cited willingness-to-pay threshold of $150,000 per QALY, but this was based on an estimated annual cost of $30,000.[50] The cost per additional QALY was lower for patients with severe AD ($75,100) than those with moderate atopic dermatitis ($125,500). Although expensive in terms of acquisition cost, dupilumab is an important therapeutic option for many patients with moderate or severe disease who have not previously had an adequate response to treatment.

Integrating New Therapies with Standard Therapies

For mild-to-moderate disease, topical agents will be sufficient for most patients. Crisaborole is a welcome topical addition for mild-to-moderate disease. With

this agent, regimens for mild to moderate disease are evolving to minimize disease symptoms with proactive plus reactive therapy. There still is a high burden of care at this level of disease with much room for improved care and patient education.

For moderate-to-severe AD, there is much undertreatment. The present systemic agents have poor benefit to risk ratios. Corticosteroids are helpful but have negative health effects. The new biologic, dupilumab, is revolutionary and tremendously important in minimizing disease impact. The other biologics and small molecule agents to follow will continue to revolutionize treatment.

Future Therapies

Clinicians and managed care need to get ready for an onslaught of new AD-targeted agents. Numerous agents are in development (Exhibit 6). Many of these target IL-4 and IL-13 like dupilumab, but a few also target IL-31 which is thought to mediate itching.

Other topical PDE4 inhibitors, including roflumilast and OPA-15406, are under investigation for mild to moderate AD. OPA-15406 ointment has a rapid onset anti-inflammatory and anti-pruritic effect and has been shown to be especially effective in selective inhibition of PDE4 subtype B.[51] Apremilast, an oral PDE4 inhibitor, FDA approved for psoriasis, is being investigated for AD. It is in Phase II studies in adults with moderate-to-severe AD and results are pending.[52]

Some features of AD may be explained by the effect of other interleukins such as IL-22 and IL-12/IL-23. IL-22 promotes hyperplasia and impairs terminal cell differentiation. Several genes are up or down-regulated by IL-22 in keratinocytes.[53] An anti IL-22 antibody (ILV-094) is being studied in moderate-to-severe AD patients. Ustekinumab (Stelara®), an anti-IL-12/IL-23 monoclonal antibody, FDA approved for psoriasis, is being investigated in moderate-to-severe AD patients; however, at least one study, which used it in combination with topical corticosteroids, did not find a benefit at 16 weeks of treatment.[54] The AD transcriptome is reversed with ustekinumab by week 32, and there has been a case report of successful treatment of refractory AD with high-dose ustekinumab.[55]

Various Janus kinase (JAK) inhibitors or jakinibs are also under investigation for AD. These agents inhibit the activity of one or more of the Janus kinase family of enzymes which interferes with cytokine signaling. Tofacitinib (Xeljanz®), which is approved as an oral formulation for rheumatoid arthritis, blocks IL-2, IL-4, IL-15, IL-21 and Th2 cell differentiation. In a Phase II trial, tofacitinib ointment 2 percent twice a day improved EASI score (-87.7% vs -29.9% with vehicle).[56] JAK inhibitors are promising in numerous other areas of dermatology, including alopecia areata, psoriasis, and vitiligo.[57]

Managed Care Issues

Current payer management of the AD drugs is minimal. Corticosteroids are largely a generic class and unmanaged. Calcineurin inhibitors are generally unmanaged but have a black box warning for lymphoma and skin cancer risk.

The entry of the first biologic injectable in the space is creating a situation analogous to the introduction of biologics for other conditions, such as rheumatoid arthritis and psoriasis. It is expected that demand for dupilumab will be high. The cost of AD treatment will be driven by dupilumab and the other biologics waiting in the wings which will increase the need for management.

Payers will need to develop a utilization management strategy to allow access to a biologic agent for those who are not responding to other therapies. Prior authorization and step edit programs will need to be developed based on labeled indication of biologics, prior therapies, and severity of disease. Tiered co-pays will also likely be implemented for biologics for AD. The current AAD guidelines do need to be updated to reflect the approval of dupilumab. Until the guidelines evolve, payers will need to depend on expert input.

Conclusion

Atopic dermatitis is a disease of barrier dysfunction and cytokine driven inflammation. The impact of AD in moderate-to-severe patients is enormous; it impacts sleep, work performance, home life, and physical and mental distress. New knowledge of pathogenesis of AD is fueling research and drug development. Dupilumab is the first approved targeted therapy for AD bringing new hope for better disease control. It is going to be a very dynamic time in the next 10 years for AD intervention as more new therapies become available. We are now beginning an exciting path for a new treatment paradigm targeting the underlying pathophysiology of AD.

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